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GENERAL PATHOLOGY

OR

THE SCIENCE OF THE CAUSES, NATURE AND COURSE
OF THE PATHOLOGICAL DISTURBANCES WHICH
OCCUR IN THE LIVING SUBJECT

BY

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AUTHOR'S PREFACE.

In making my preparations for the publication of an eighth edition of my "Treatise on Pathological Anatomy," I hesitated for a long time in regard to what method of revision I should adopt. During recent years a number of manuals of pathological anatomy have been published, and the authors of these seem to have laid stress upon the point that a text-book intended for the use of medical men should deal with the subject-matter in the most concise manner possible; they believed, evidently, that compendious treatises of this nature would tend to promote the study of pathological anatomy, and would at the same time render the student's task easier. I carefully examined a number of compends of pathological anatomy which had been written from this point of view, but they failed to convince me that this was the most useful manner of treating the subject. In the first place, it is not possible, within the limits of a small compend, to treat general pathology and pathological anatomy in a scientific manner. Then, in the next place, it is extremely difficult, owing to the richness of the material at our disposal, to avoid treating the subject in such a manner that the book, when completed, shall not present the characteristics of a mere catalogue of facts, which would scarcely convey to the reader's mind a clear conception of the processes that take place in the living body when it or any of its organs are diseased, and which, furthermore, would compel the beginner to merely commit to memory those things which, by the aid of his reasoning power, he should make a permanent and useful part of his medical knowledge.

It is possible that if a compend were gotten up in the form of a catechism, it might prove helpful to a certain number of students in acquiring a knowledge of the principles of general pathology and pathological anatomy. Nevertheless I am disposed to believe that the number of those who would derive satisfaction from such a catechism must indeed be small. General pathology and pathological anatomy should constitute the foundations of that knowledge which is to enable the practitioner of medicine to interpret correctly the symptoms of disease as they present themselves before him at the patient's bedside. It must be conceded, I think, that simply a knowledge of the definitions given to the technical terms commonly employed in describing different pathological processes that take place in the living body, or merely a superficial insight into the pathological processes which affect individual organs and tissues, can scarcely suffice to furnish the practitioner with the fundamental knowledge which he requires for the satisfactory study of clinical medicine. He might be able, it is true, when called to treat a patient who presented certain well-defined symptoms of disease—as, for example, those belonging to an inflammation of an important organ—to form an approximate idea of the nature of this disease, and at the same time he would also probably take satisfaction in the thought that he had already been instructed in regard to the occurrence of this very malady in this particular organ. But he certainly would not be able to form a clear conception of the essential nature of the entire process, or to analyze all the little pathological features which are dependent upon the peculiar construction of the organ affected; in a word, he would not be able to interpret, in its full breadth and depth, the significance of the disease under observation. In his endeavors to understand each new type of disease he would, by reason of his lack of a proper training in the fundamental principles of medicine, find his pathway constantly strewed with difficulties, and he would be forced in a slow and plodding fashion to commit to memory the sequence of symptoms as they occur in any given disease. Then, besides, he would fail to grasp the connection between the latter and other correlated symptoms. On the other hand, if he had previously received proper instruction in the fundamental knowledge required, he would at once be able to understand correctly the nature of the malady which he has been called to treat.

Bearing all these things in mind, I felt as if it were perfectly clear what my aim ought to be in preparing this new edition of my "Treatise on Pathological Anatomy." In the first place, it seemed to me that I should strive to perfect the knowledge of the mode of origin, nature, and significance of diseases as they occur in the living body, and consequently that I should make such improvements and alterations in the text as would carry out this idea. As a matter of course, in making this revision I did not forget for a moment that descriptions of histological and pathologico-anatomical alterations must continue to form the foundation-work of the book. Knowing, also, from experience how greatly good illustrations aid the reader in understanding the nature of these alterations, it seemed to me that I ought to provide a certain number of additional cuts, carefully prepared. At the same time I felt as if more space than was given to these matters in the preceding editions should be allotted to the consideration of pathological processes—their causes, their mode of origin, the course which they pursue, and their sequelæ.

In performing the task which I had thus set before me I found that extensive alterations were necessary, especially in that part of the work which treats of general pathology. On the one hand I found it necessary either to greatly alter or actually to rewrite certain chapters, while on the other I was obliged even to introduce entirely new chapters. In remodelling this general portion of the work special consideration has been given to the subjects of general etiology of diseases and pathological physiology, and in harmony with these alterations it has seemed to me advisable to change also the title of this general part. Accordingly I have abandoned the former title, "General Pathological Anatomy," and have substituted for it that of "General Pathology." The present work, it is true, does not cover the entire field of general pathology, but nevertheless it does treat of all those portions of the subject which are ordinarily taught, at least in the German universities, by the chairs of pathological anatomy and general pathology.

The section which deals with the causes, mode of origin, and course of diseases has, with the exception of a few pages, been entirely rewritten and greatly amplified; and I have gone more thoroughly in the present edition than I did in the earlier ones into the subject of the origin of diseases from poisoning and from infection, hoping thereby to provide the beginner with a thoroughly clear and simple description of the pathological changes which take place in these diseases. Furthermore, I have given full consideration to the subject of the dissemination of pathological foci throughout the body by means of the processes known as metastasis and embolism, by means of poisoning, or by means of the extinction of certain glandular functions; and at the same time I have explained the relations of these foci to pathologically altered functions. Among the diseases which owe their origin to the extinction or modification of certain glandular functions I have given careful consideration to diabetes mellitus, to the cachexia which results from a withdrawal of the influence exerted by the thyroid gland upon the economy, to myxœdema, to cretinism, and to Addison's disease.

I have introduced special chapters on the protective mechanisms and forces, and on the healing powers of the human body; on certain inherited and acquired weaknesses or predispositions; on idiosyncrasy and immunity; and on the acquisition of immunity through the fact of one's having already experienced an attack of the disease, or through inoculation; and it is my hope that these chapters will not only supply the practical needs of the medical practitioner, but will also serve to increase the existing stock of knowledge in regard to the origin, course, and essential nature of diseases, and particularly of those which are due to infection and poisoning.

The chapter on the causes of internal diseases and on the inheritance of certain pathological conditions will, I think, be found to supply not only a clearer bird's-eye view of the subject, but also at the same time more complete information than did the same chapter in the earlier editions.

The section relating to disturbances of the circulation remains unchanged in its general features, but it has in many respects been made more complete than it formerly was; and, besides, it has been furnished with new illustrations.

In the section relating to retrograde disturbances of nutrition and infiltrations of the tissues, the chapter devoted to hypoplasia, agenesia, and atrophy and that relating to pigment-formation are the ones which have been remodelled to the greatest extent. In the section devoted to hypertrophy and regeneration I have introduced all the alterations and additions which the investigations of recent years in regard to these processes rendered necessary.

The section on inflammation has been entirely rewritten, and the definition which I now give of this process is the same as that which I suggested two years ago and published in pamphlet form. I am well aware that my views in regard to the nature of inflammation will not be generally accepted, and yet I cannot help hoping that, in giving this new explanation of pathological changes which have received such varied interpretation at the hands of different authorities, I may have succeeded in furnishing satisfactory proof that, on the basis of the views here set forth, all the different processes which play a part in inflammation may be arranged in comprehensive groups; and, furthermore, that the separation of the reparative processes of proliferation from those which belong more strictly to inflammation—which latter are characterized by a degeneration of the tissues, coupled with an exudation of pathological fluid products—is in harmony with the practical needs of the physician as well as with the unprejudiced requirements of science. In describing the healing processes which take place in the course of an inflammation, the formation of granulations, the resorption of necrosed tissues and exudations, and the substitution, in their place, first of granulation tissue and then of cicatricial tissue, I have striven by the aid of numerous pictorial illustrations to make it easier for the student to understand these important processes, and at the same time I have endeavored to manage my descriptive text in such a way that it should throw light upon those diseases which are most commonly encountered in actual medical practice.

The sections which relate to tumors and malformations remain fundamentally the same as they were in the previous edition, and yet in both of these sections I have rewritten the portions which refer to the general aspects of these subjects, and at the same time I have altered, improved, and amplified many of the remaining paragraphs in these sections; this statement being particularly true of the paragraphs relating to cystomata, teratomata, and transposition of tissues.

In the section devoted to parasites I have given due weight to the results of recent investigations, at least so far as they seemed to me to be thoroughly established. I have treated the infectious granulation tumors as heretofore in the section devoted to parasitic diseases, for it would scarcely be possible to acquire a complete understanding of their nature and significance unless full account were taken of the relationship which exists between their peculiarities and the special nature of the exciting cause.

As a result of all these alterations and additions this general part of my text-book has increased in bulk; but, as I have already said, I believe that, owing to the wealth of material which must be treated in a text-book of general pathology, it would scarcely be possible to handle the subject more concisely unless important matters should be entirely omitted, and unless the idea of explaining fully the phenomena of disease in the living subject should be abandoned.

But, after all, the extent of the text which the beginner must actually study is less than one might at first suppose it to be, for the illustrations, which have been increased in number by the addition of seventy-two, and the text printed in small type occupy a good deal of space in the volume.

E. ZIEGLER.

FREIBURG IM BREISGAU, November, 1894.

EDITORIAL NOTE.

It has been thought best to omit from this edition the bibliographical lists which are scattered throughout the original work. They occupy a great deal of space, and consequently would add considerably to the bulk of the present volume; they refer almost exclusively to books and articles published in the French, Italian, or German language, and would therefore prove of value to comparatively few students or practitioners in this country; and, finally, the publication of these additional two hundred pages would necessarily add considerably to the cost of the work. For all these reasons it seemed advisable to leave them out altogether.

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CONTENTS.

PAGE

PREFACE iii

SECTION I.—Introduction.—Health and Disease.—Problems of General Pathology and Pathological Anatomy 1

SECTION II.—Cause, Origin, and Course of Diseases; General Considerations.

- I. Origin of Diseases through External Pathological Influences 8
  - 1. Origin of Diseases through Deficiency of Food and of Oxygen; by Fatigue; by Heat and Cold; by Changes of the Atmospheric Pressure; by Electrical and by Mechanical Influences. 8
  - 2. Origin of Diseases through Intoxication 17
  - 3. Origin of Diseases through Infection or Parasitism.—Miasms and Contagions.—Vegetable and Animal Parasites 28
- II. Metastasis and Embolism, and their Importance in the Etiology of Lymphogenous and Hæmatogenous Diseases 40
- III. Local and General Diseases, and their Relations to One Another.—Intoxication after Infection, and Auto-intoxication.—Injurious Effects of Diseases of One Organ on Other Organs, and on the General Organism.—Diseases Caused by the Withdrawal of the Functions of Certain Glands 48
- IV. Fever and its Significance 62
- V. The Natural Protective Mechanisms, Protective Forces, and Healing Powers of the Human Organism, and their Action 68
- VI. Congenital and Acquired Predisposition.—Idiosyncrasy and Immunity.—The Acquiring of Immunity.—Immunizing Inoculations .. 77
- VII. The Intrinsic Causes of Disease and the Inheritance of Pathological Conditions 88

SECTION III.—Disturbances in the Circulation of the Blood and of the Lymph.

- I. General Circulatory Disturbances Dependent upon Changes in the Function of the Heart, Changes in the General Vascular Resistance, and Changes in the Mass of the Blood 103
- II. Local Hyperæmia and Local Anæmia 109
- III. Coagulation, Thrombosis, and Stasis 114
- IV. Œdema and Dropsy 129
- V. Hæmorrhage and the Formation of Infarcts 134
- VI. Lymphorrhagia 140

PAGE

SECTION IV.—Retrograde Disturbances of Nutrition and Infiltrations of the Tissues.

I. On Retrograde Disturbances of Nutrition and Infiltrations of the Tissues in General 142
II. Death 143
III. Necrosis 145
IV. Hypoplasia, Agenesia, and Atrophy 156
V. Cloudy Swelling and Hydropic Degeneration of Cells 166
VI. Lipomatosis, Fatty Atrophy, and Fatty Degeneration 168
VII. Glycogen-deposit in the Tissues under Pathological Conditions 174
VIII. Mucous and Colloid Degenerations 176
IX. Amyloid Degeneration and Amyloid Concretions 180
X. Hyaline Degeneration of Connective Tissue 186
XI. Calcification and the Formation of Concretions and Calculi 188
XII. Pigment-formation in the Tissues 197
XIII. Cyst-formation 213

SECTION V.—Hypertrophy and Regeneration of the Tissues and Organs.

I. General Considerations Concerning the Processes called Hypertrophy and Regeneration, and the Cellular Changes that Accompany Them 217
II. The Processes of Hyperplasia and Regeneration in the Various Tissues 239
III. Metaplasia of the Tissues 257

SECTION VI.—Inflammation and the Associated Processes of Repair.

I. Acute Inflammation and its Various Forms 260
II. The Processes of Repair Associated with Inflammation.—Formation of Granulation and Cicatricial Tissues.—Resorption of Exudates and Tissue-necroses, and Substitution of Connective Tissue for Them. 281
III. Phagocytosis Occurring in the Course of Inflammations, and the Formation of Giant Cells around Foreign Bodies.—Chemotaxis .. 294
IV. Chronic Inflammations 297

SECTION VII.—Tumors.

I. General Considerations 303
II. The Different Varieties of Tumors ....
  1. Tumors which Develop from the Middle Embryonic Layer.—Connective-tissue Tumors.
    (*a*) Fibroma 312
    (*b*) Myxoma 314
    (*c*) Lipoma 315
    (*d*) Chondroma 316
    (*e*) Osteoma 317
    (*f*) Angioma 320
    (*g*) Myoma 327
    (*h*) Glioma and Ganglionic Neuroglioma 330

PAGE
(i) Neuroma 332
(k) Lymphadenoma and Lymphosarcoma 334
(l) Sarcoma 336
(m) Mixed Forms of the Connective-tissue Tumors 348
2. Tumors whose Structure comprises Epithelium as well as Connective Tissue and Blood-vessels.—Epithelial Tumors.
(a) Preliminary Remarks 351
(b) The Adenomata and their Relations to Glandular Hypertrophies and Carcinomata 352
(c) Carcinoma 357
(d) Epithelial Cystomata.—Cystadenoma and Cystocarcinoma 371
3. Teratomata and their Relations to Monogerminal and Bigerminal Implantations and to Remains of Fœtal Structures 381

SECTION VIII.—Disturbances of Development and the Resulting Malformations.

I. General Considerations in Regard to Disturbances of Development and the Origin of Malformations 386
II. Special Malformations in Man.
1. Arrests of Development in a Single Individual.
(a) Arrest in the Development of all the Embryonic Elements 394
(b) Deficient Closure of the Cerebrospinal Canal and the Accompanying Malformations of the Nervous System 396
(c) Malformations of the Face and Neck 405
(d) Faulty Closure of the Abdominal and Thoracic Cavities, and the Accompanying Malformations 408
(e) The Malformations in the External Genitalia and the Anal Region Caused by Arrested Development 410
(f) Malformations of the Extremities due to Arrest of Development 412
2. Abnormal Positions of the Internal Organs and of the Extremities 415
3. Malpositions the Result of Excessive Growth or Multiplication of Organs or Parts of the Body 416
4. True and False Hermaphrodism 418
5. Double Malformations.
(a) Complete Duplication of the Axial Structures 423
(b) Partial Duplication of the Axial Structures 427
(c) Triple Monsters 430

SECTION IX.—Fission-fungi which Exist as Parasites and the Diseases Caused by Them.

I. General Considerations in Regard to the Schizomycetes or Fission-fungi.
1. General Biology of the Fission-fungi 431
2. General Considerations Concerning the Pathogenic Fission-fungi and their Behavior in the Human Organism 440
3. General Considerations in Regard to the Examination of Fission-fungi 443

PAGE

II. The Different Forms of Fission-fungi and the Infectious Diseases Caused by Them.
  1. The Cocci and the Morbid Processes Caused by Them.
    (a) Forms of Growth of the Cocci.—Saprophytic Cocci...... 446
    (b) Pathogenic Cocci.................................... 448
  2. The Bacilli and the Morbid Processes Caused by Them.
    (a) Vegetative Forms and Method of Multiplication of the Bacilli.—Non-pathogenic Saprophytic Bacilli............ 459
    (b) Pathogenic Bacilli.................................... 462
  3. The Spirilla and the Morbid Processes Caused by Them.
    (a) Non-pathogenic Saprophytic Spirilla................... 516
    (b) Pathogenic Spirilla.................................... 517

SECTION X.—Mould-fungi and Yeast-fungi, and the Pathological Tissue-changes Caused by Them.............................. 523

SECTION XI.—The Animal Parasites.

I. Arthropoda.
  1. Arachnida.. 534
  2. Insects.. 537
II. Vermes (Worms).
  1. Nematodes (Roundworms)................................ 539
  2. Trematodes (Sucking-worms)............................ 549
  3. Cestodes (Tapeworms).................................. 552
III. Protozoa.. 563

LIST OF ILLUSTRATIONS.

PAGE
1. Lightning-figures on the shoulder, breast, and arm 14
2. Multiple emboli in the branches of the pulmonary artery 41
3. Temperature-curve in a continued remittent fever with a slowly increasing and a very gradually decreasing temperature 63
4. Temperature-curve of a continued fever with rapid increase and rapid decline of temperature 64
5. Temperature-curve of an intermittent tertian fever 64
6. Recent hæmorrhagic infarct of the lung 114
7. Section through a red thrombus in a muscular vein 115
8. Section of a white thrombus in the vena cava inferior 116
9. Section of a mixed thrombus of the aorta 116
10. Quickly flowing blood-stream 118
11. Somewhat retarded blood-stream 118
12. Greatly retarded blood-stream 118
13. Thrombus-formation in the heart 122
14. Thrombosis of the femoral and of the saphenous vein 123
15. Remains of a thrombus of the right femoral vein 125
16. Pulmonary infarct with obliteration of the artery in the process of healing 126
17. Remains of an embolic plug of a branch of the pulmonary artery 127
18. Embolus of an intestinal artery with suppurative arteritis 127
19. Stasis from venous hyperæmia in the vessels of the corium and of the papillæ of the toes 128
20. Longitudinal section through œdematous muscle-fibres 130
21. Anæmic infarct of the kidney 137
22. Recent hæmorrhagic infarct of the lung 138
23. Necrosis of the epithelium of the uriniferous tubes 146
24. Croupous membrane from the trachea 149
25. Waxy degeneration of muscular fibres 149
26. Section of uvula after destruction of its epithelial covering by diphtheria 150
27. Tissue from a focus of tubercular disease, showing bacilli and a limited area of cheesy degeneration 151
28. Section through the epidermal and papillary portions of a cat's paw, a short time after it had been burned with fluid sealing-wax 152
29. Dry gangrene of the toes from arteriosclerosis 153
30. Skeleton of a female dwarf, thirty-one years of age 155
31. Skeleton of a female dwarf, fifty-eight years of age 155

PAGE
32. Head of Helene Becker (microcephalic) 156
33. Brain of Helene Becker 156
34. Hypoplasia of the os innominatum from coxitis 157
35. Hypoplasia and microgyria of the left cerebral hemisphere 158
36. Hypoplasia of the uterus with well-developed ovaries 158
37. Hypoplasia of the small intestine 159
38. Agenesia of the respiratory parenchyma of the lung 159
39. Juvenile muscular atrophy 160
40. Excentric atrophy of the lower ends of the tibia and fibula, with osteoporosis 161
41. Senile atrophy of the calvarium 161
42. Section of an atrophied muscle from a case of progressive muscular atrophy 162
43. Senile atrophy of the kidney 162
44. Arteriosclerotic atrophy of the kidney 164
45. Pressure atrophy of the spinal column 165
46. Facial hemiatrophy 166
47. Cloudy swelling of liver-cells 166
48. Cloudy swelling of kidney epithelium 167
49. Hydropic degeneration of epithelial cells 167
50, 51. Hydropically degenerated muscular fibres 168
52. Fat-containing liver-cells 170
53. Fatty degeneration of the muscular tissue of the heart 170
54. Fatty and amyloid degeneration of the kidney 171
55. Cholesterin plates and margarin needles 174
56. Mucous degeneration of epithelial cells 176
57. Mucous degeneration of connective tissue of aortic valves 176
58. Colloid in a specimen from an enlarged thyroid gland 178
59. Section of a contracted kidney, showing arteriosclerosis and masses of colloid in the uriniferous tubules 179
60. Section of amyloid liver stained with iodine 181
61. Section of amyloid liver treated with methyl violet and acetic acid 181
62. Section of an amyloid kidney 183
63. Amyloid swelling of the reticulum of a lymphatic gland 184
64. Corpora amylacea 185
65. Hyaline degeneration of the blood-vessels of an atrophic lymph-gland. 186
66. Hyaline degeneration of the connective tissue of the myocardium 186
67. Calcification of the media of the aorta 189
68. Calcified ganglion-cells from the brain of a demented person 189
69. Calcareous concretions 190
70. Section of a psammoma of the dura mater, with calcareous formations. 190
71. Deposits of urates in the knee-joint in gout 191
72. Needle-shaped crystals of urate of soda in the articular cartilage 191
73. Gouty urates of the hand 192
74. Faceted concretions from the gall-bladder 193
75. Transverse section of cholesterin calculus after the removal of all the cholesterin 194
76. Uric-acid infarction of the kidney 195
77. Coral-shaped calculus of oxalate and phosphate of lime 196

PAGE
78. Transverse section of two stones from the bladder, closely fitted together, composed of urate of soda and ammonio-magnesium phosphate 196
79. Hairy pigmented mole over back and hips 197
80. Pigmented cells of the skin from a case of Addison's disease 198
81. Cells containing amorphous blood-pigment; rhombic plates and needles of hæmatoidin 201
82. Cells containing hæmosiderin and hæmatoidin 201
83. Cells containing pigment-granules in the lymph-glands 203
84. Infiltration of trabeculæ of liver-cells with yellow hæmosiderin granules 204
85. Hæmochromatosis of the liver 205
86. Hæmatogenous deposit of iron in the kidney 206
87. Icterus of the liver from compression of the ductus choledochus. 209
88. Icterus of the lymph-glands in jaundice due to obstructed outflow of bile 210
89. Icterus of the kidney in jaundice due to obstructed outflow of bile 210
90. Deposits of silver in the pyramidal portion of a rabbit's kidney 213
91. Multiple cysts in the head of the epididymis 214
92. Cyst of the pancreas from dilatation of a branch of Wirsung's duct 214
93. Dropsy of the Fallopian tube, with adhesions 215
94. Elephantiasis neuromatosa 217
95. Elephantiasis lymphangiectatica 218
96. Leontiasis ossea 219
97, 98. Akromegaly of Erb and Arnold 220
99. Ichthyosis congenita 221
100, 101. Cornu cutaneum 222
102. Head of a hairy woman 222
103. Hypertrophy of the left ventricle in aortic-valve disease 223
104. Hypertrophy of incisor tooth of a white rat 224
105–120. Nuclear changes in cell-division 228
121–126. Nuclear changes in cell-division 230
127. Nuclear changes in cell-division 231
128, 129. Giant cells from sarcoma of the tibia 232
130. Regeneration of epithelium 240
131. Healing of an ulcer of the intestine 241
132. Development of blood-vessels by formation of offshoots 242
133. Vessels of the papillary layer whose endothelial cells are in process of growth 243
134. Proliferating periosteum 244
135. Isolated cells from a granulating wound 245
136. Development of connective tissue from fibroblasts 246
137. Periosteal cartilage-formation 246
138. Formation of osteoid trabeculæ from the proliferating periosteum 247
139. Bone-formation by heaping up of osteoblasts from old bone 247
140. Section from the centre of development of a mesenteric gland 249
141. Portions of muscle-fibre at various stages of regenerative growth 252
142. Old and newly formed nerve-fibres 255
143. Cross-section of a nerve-bundle just above a wound made four months previously 256
144. Amputation neuroma of the sciatic nerve 256

PAGE
145. Metaplasia of cartilage in reticular tissue 258
146. Bone-formation from connective tissue 259
147. Inflamed human mesentery 262
148. Section through the border of a blister 266
149. Recent interstitial hepatitis 267
150. Parenchymatous nephritis, with necrosis of epithelium of uriniferous tubules 267
151. Superficial catarrhal inflammation of a bronchus 268
152. Inflammatory œdema of the kidney, with catarrh of the uriniferous tubules 270
153. Catarrhal secretion of various mucous membranes 271
154. Acute hæmorrhagic fibrinous inflammation of the trachea 272
155. Croupous membrane from the trachea 272
156. Section of the uvula, showing stratified fibrin membrane, in a case of diphtheritic croup 273
157. Adhesive pericarditis 274
158. Croupous hepatization of lung 274
159. Purulent bronchitis, peribronchitis, and peribronchial bronchopneumonia 275
160. Section of a smallpox pustule 276
161. Embolic abscess of the intestinal wall 276
162. Suppuration and necrosis of the mucous membrane of the large intestine in dysentery 277
163. Necrosis of the epithelium of the epiglottis 279
164. Bacillary diphtheritis of the large intestine 280
165. Section of the uvula in pharyngeal diphtheria 280
166. Isolated cells from a wound-granulation 284
167. Blood-vessel from the deep layer of the skin after painting with iodine 285
168. Wound-granulations from an open wound, with fibrino-purulent surface deposit 285
169. Repair of an incised wound of the skin united by suture 287
170. Cicatrix of skin six months after incision 288
171. Fibrin-deposit and beginning formation of granulations in pericarditis 289
172. Formation of granulations within a fibrinous deposit in pericarditis 290
173. Development of embryonal tissue in a thrombosed femoral artery 291
174. Recent hæmorrhagic infarct of the lung 291
175. Healing infarct of the lung 292
176. Callosity of heart—fibroid degeneration 293
177. Granular cells in a focus of degeneration of the brain 294
178. Phagocytes from granulating tissue 295
179. Pigmented granule-spheres in a lymphatic gland 295
180. Dog's hair encapsulated in subcutaneous tissue 296
181. Old necrosis of the femur 298
182. Stone-cutter's lung with bronchopneumonic fibrous nodules 299
183. Condyloma acuminatum 299
184. Periosteal hyperostosis of the tibia, at the base of a chronic ulcer of the leg 300
185. Transverse section through the mucosa and submucosa of an atrophic large intestine 301

PAGE
186. Induration and atrophy of the renal tissue in chronic nephritis....... 301
187. Connective-tissue hyperplasia and development of bile-ducts in chronic hepatitis.......... 302
188. Spongy carcinoma of the mucous membrane of the uterus........... 304
189. Section through a nodular angiosarcoma of the thyroid gland....... 305
190. Primary cancer of the gall-bladder, with an impacted stone in this cavity.......... 307
191. Section through a primary carcinoma of the liver.................. 308
192. Metastatic carcinoma of the lung.................................. 309
193. Metastatic sarcoma of the liver................................... 310
194. Sarcoma recurrent in an amputation stump......................... 311
195. Section through an œdematous fibroma of the uterus............... 312
196. Paracanalicular fibroma of the breast............................. 313
197. Cells from a myxoma of the periosteum............................ 314
198. Section of a myxosarcoma.. 315
199. Section through a chondroma of the ribs........................... 316
200. Multiple eburneous exostoses of the frontal bone.................. 318
201. Cartilaginous exostosis of the tibia.............................. 318
202. Eburneous osteoma of occipital bone............................... 319
203. Dilated capillaries from a telangiectatic tumor of the brain.......... 321
204. Section through an angioma simplex hypertrophicum cutaneum et subcutaneum.......... 322
205. Angioma cavernosum cutaneum congenitum............................ 322
206. Section through cavernous angioma of the liver in process of active growth.......... 323
207. Angioma arteriale plexiforme of the frontal and angular arteries..... 323
208. Lymphangioma cavernosum subcutaneum............................... 324
209. Pigmented nævus of the back, buttocks, and thighs................. 325
210. Section through a fleshy wart..................................... 326
211. Section through two papillæ of a papillomatous fleshy wart.......... 326
212. Section through a leiomyoma, showing the nuclei cut both longitudinally and transversely.......... 327
213. Subcutaneous angiomyoma of the back............................... 328
214. Cells from a rhabdomyoma.. 329
215. Glioma of the cerebrum.. 330
216. Section from a nodular neuroglioma ganglionare of the cerebrum.... 331
217. Amputation neuroma of the ischiatic nerve......................... 332
218. Nerves from a cirsoid neuroma which presented a close resemblance to elephantiasis.......... 333
219. Cirsoid neuroma of the sacral region.............................. 334
220. Section through a sarcoma of the intermuscular connective tissue of the neck.......... 338
221. Section through a lymphosarcoma of the mucous membrane of the nose 338
222. Section through a fungoid large round-celled sarcoma of the skin of the leg.......... 339
223. Section of a sarcoma of the breast, with variously shaped cells....... 339
224. Spindle-cells from a sarcoma of the cheek......................... 340
225. Cells from a medullary giant-celled sarcoma of the tibia............ 340
226. Section through an endothelioma of the pia mater and cerebral cortex 341

PAGE
227. Endothelioma of the dura mater 342
228. Section through a nodular angiosarcoma of the thyroid gland 343
229. Section through an alveolar sarcoma of a lymphatic gland 343
230. Section through a melanotic alveolar sarcoma of the skin 344
231. Section of a psammoma of the dura mater 345
232. Petrifying large-celled sarcoma of the tibia 346
233. Sarcoma myxomatodes 346
234. Section through a myxosarcoma (cylindroma) 347
235. Cluster of blood-vessels having hyaline sheaths and hyaline processes: from a cylindroma 347
236. Chondromyxosarcoma of the parotid 348
237. Osteoid sarcoma of the ethmoid bone 349
238. Section through an osteoid chondroma 350
239. Alveolar adenoma of the breast 353
240. Tubular adenoma of the breast 353
241. Adenoma tubulare papilliferum of the kidney 354
242. Section of a benign polyp of the large intestine ... 354
243. Hyperplasia of the mucous membrane of the uterus 355
244. Section of a glandular polyp of the stomach 355
245. Section through a tubular adenoma destruens of the stomach 356
246. Tubular adenocarcinoma of the rectum 358
247. Adenocarcinoma of the uterus 358
248. Section through a cancer of the skin in an early stage of development 359
249. Section through a carcinoma of the breast 360
250. Epithelial plug from a cancer of the skin 361
251. Section of a carcinoma simplex of the breast 363
252. Gelatinous carcinoma of the breast 364
253. Myxomatous carcinoma of the stomach 365
254. Carcinoma cylindromatosum, showing hyaline degeneration of the epithelium 365
255. Enlarged dropsical cancer-cells 366
256. Primary carcinoma of the liver 367
257. Section through an aggregation of very young cancer-cells, lodged like an embolus within a capillary of the liver 368
258. Metastatic cancer development in the liver-capillaries 368
259. Cystoma of the ovary, partly simple, partly papillary in character 371
260. Section of a multilocular cystoma of the ovary 372
261. Section of a papillary cystoma of the ovary 372
262. Section through an adenocystoma of the testicle ... 373
263. Section of multilocular cystoma of the liver 373
264. Section of cystoma of the kidney 374
265. Longitudinal section of a congenital cystic kidney, with small cysts 374
266. Papillary cystoma of the breast 375
267. Section of a papillary cystadenoma of the ovary 376
268. Papillary cystoma of the ovary............................ 378
269. Section of a papillary adenocystoma of the ovary......... 379
270. Intracanalicular fibroma of the breast........................... 379
271. Papillary cystoma or intracanalicular papillary fibroma of the breast 380
272. Congenital adenocystoma of the testicle........................ . . 381

PAGE
273. Wall of an ovarian dermoid cyst 382
274. Spina bifida occulta 385
275. Malformation of the head, due to adhesions of the membranes to the frontal region 388
276. Malformation of the face, caused by amniotic adhesions and pressure 388
277. A hand stunted by amniotic adhesions 389
278. A hand stunted and misshapen by pressure 389
279. Portion of a mole, presenting the form of a bunch of grapes 395
280. Fœtus entirely inclosed by fibrous membranes 396
281. Craniorachischisis, with total absence of the brain and spinal cord... 397
282. Rachischisis partialis 397
283. Spina bifida sacralis 399
284. Myelomeningocele sacralis 399
285. Anencephalia et acrania 402
286. Cranioschisis 402
287. Partial agenesia of the cranial bones 403
288. Hydrencephalocele occipitalis 404
289. Synophthalmia or cyclopia 404
290. Cranial cavity of a synophthalmus microstomus 405
291. Double cheilo-gnatho-palatoschisis 406
292. Agnathia and synotia 406
293. Hernia funiculi umbilicalis 408
294. Fissura abdominis et vesicæ urinariæ 410
295. Hypospadias 410
296. Epispadias 410
297. Complete absence of urethra and external genitals 411
298. Amelus 413
299. Micromelus 413
300. Sympus apus 413
301. Sympus dipus 413
302, 303. Perochirus 414
304, 305. Peropus 414
306. Polydactylism with duplication of hand 417
307. Polydactylism and syndactylism of hand 417
308. Polydactylism and syndactylism of foot 417
309. Hermaphrodismus verus lateralis 420
310. External genitalia of a female false hermaphrodite 422
311. Thoracopagus tribrachius tripus 423
312. Craniopagus parietalis 423
313. Ischiopagus 424
314. Acardiacus acephalus 425
315. Acardiacus acormus 425
316. Epignathus 426
317. Diprosopus distomus tetrophthalmus diotus 428
318. Cephalothoracopagus or syncephalus with Janus-head 428
319–321. Dipygus parasiticus 429
322. Streptococcus colonies upon and in the epithelium of the vocal cord.. 440
323. Gelatin plate containing colonies of small bacilli 444
324. Streptococcus from puerperal peritonitis 446

PAGE
325. Micrococcus colonies ... 446
326. Cocci grouped in tetrads (merismopedia) ... 446
327. Sarcina ventriculi ... 446
328. Metastatic aggregation of micrococci in the liver ... 449
329. Endocarditis pustulose caused by staphylococcus pyogenes aureus ... 449
330. Streptococcus pyogenes ... 451
331. Pectoral muscle beset with large numbers of streptococcus pyogenes 452
332. Colonies of streptococcus erysipelatis ... 453
333. Section of the skin in erysipelas bullosum ... 454
334. Gonococci ... 455
335. Diplococcus pneumoniæ of Weichselbaum and Fränkel ... 456
336. Bacillus subtilis ... 460
337. Clostridium butyricum ... 460
338. Capillaries of liver containing numbers of anthrax-bacilli and a few leucocytes ... 463
339. Anthrax-bacilli containing spores, and free spores that have escaped from the bacilli ... 463
340. Section through an anthrax-pustule ... 464
341. Section through a portion of anthrax-pustule containing bacilli ... 465
342. Bacillus of typhoid fever ... 467
343. Section through swollen Peyer's plaque in typhoid fever ... 469
344. Bacillus pneumoniæ of Friedländer ... 471
345. Nail-shaped stab-culture of Friedländer's pneumo-bacillus ... 471
346. Tubercle-bacilli ... 476
347. Tissue-changes produced by a recent invasion of the tubercle-bacilli .. 478
348. Giant cell containing bacilli, from a tubercle ... 478
349. Tubercle from a fungous granulation of bone ... 479
350. Tissue from a focus of tubercular disease, showing bacilli and cheesy degeneration ... 480
351. Primary tubercular nodules in the lungs, with beginning tubercular lymphangitis ... 482
352. Subepithelial tubercular granulations and scattered tubercles in the large intestine ... 483
353. Large solitary tubercles of the pia mater ... 484
354. Section through skin affected with lupus ... 484
355. Tubercle of bone in advanced stage ... 485
356. Section through tubercular lung ... 486
357. Tubercular eruption in a lymph-gland ... 487
358. Tuberculosis omenti ... 488
359. Hæmatogenic miliary tuberculosis of the liver ... 489
360. Growths from the pleura in bovine tuberculosis ... 491
361. Section of a syphilitic initial necrosis ... 493
362. Condyloma latum ani ... 494
363. Meningo-encephalitis syphilitica gummosa ... 495
364. Gumma of the liver ... 496
365. Syphilitic ulceration of the larynx 497
366. Congenital syphilis of the lungs 497
367. Tissue from a leprosy-nodule 498
368. Two giant cells with vacuoles containing bacilli, from a leprous growth ... 498

PAGE
369. Section through a leprous skin-nodule 499
370. Leontiasis leprosa 500
371. Lepra anæsthetica ulcerosa 501
372. Lepra anæsthetica mutilans 502
373. Bacillus of rhinoscleroma 505
374. Section of rhinoscleromatous tissue 506
375. Cells with hyaline degeneration and hyaline globules from rhinoscleromatous tissue of the vocal cord and nose 506
376. Section through an infected abdominal muscle of a guinea-pig 507
377. Plate-culture of the bacillus of swine-erysipelas 508
378. Actinomyces hominis 511
379. Section from a tongue affected with actinomycosis 511
380. Actinomycosis of the lung 512
381. Spirillum sive vibrio rugula and spirillum undula 516
382. Cholera-spirilla 517
383. Stab-culture of Finkler-Prior bacillus 521
384. Spirochaete Obermeieri 522
385. Hyphæ, conidia, and epithelial cells from a fresh specimen of favus 524
386. Conidia spores from aphthæ of tongue 524
387. Saccharomyces ellipsoideus 525
388. Section through an aphthæ-covered œsophagus of a small child 526
389. Mucor corymbifer in fructification 527
390. Hyphæ of aspergillus fumigatus 527
391. Favus scutulum 529
392. Hair affected with favus 531
393. Culture of trichophyton tonsurans 532
394. Female itch-mite 534
395. Section of the skin in scabies 535
396. Leptus autumnalis 535
397. Acarus folliculorum hominis 536
398. Ixodes ricinus 536
399. Head end of pentastoma denticulatum 536
400. Male of dermatophagus communis 537
401. Male of dermatocoptes communis 537
402. Female pediculus capitis 538
403. Male pediculus pubis 538
404. Female pediculus vestimentorum 538
405. Gastrophilus equi 539
406. Ascaris lumbricoides 540
407. Egg of ascaris lumbricoides 540
408. Oxyuris vermicularis 541
409. Eggs of oxyuris vermicularis 541
410. Male of anchylostoma duodenale 543
411. Cephalic end of anchylostoma duodenale 543
412. Eggs of anchylostoma duodenale 543
413. Female of anguillula stercoralis 544
414. Trichocephalus dispar 545
415. Egg of trichocephalus dispar 545
416. Sexually mature trichinæ 546
417. Encapsulated muscle-trichinæ 546

PAGE
418. Filaria or dracunculus medinensis 548
419. Embryo of filaria Bancrofti 548
420. Distoma hepaticum 549
421. Eggs of distoma hepaticum 550
422. Distoma lanceolatum 551
423. Eggs of distoma lanceolatum 551
424. Distoma hæmatobium 552
425. Eggs of distoma hæmatobium 552
426. Head of tænia solium 553
427. Segments of tænia solium 553
428. Proglottides of tænia solium 553
429. Sexual apparatus of tænia solium 554
430. Eggs of tænia solium 555
431. Cysticercus cellulosæ 555
432. Cysticerci in the heart of a pig 555
433. Tænia saginata 556
434. Head of tænia saginata 556
435. Segment of tænia saginata 556
436. Tænia echinococcus 558
437. Brood-capsules of tænia echinococcus 558
438. Section of echinococcus multilocularis 559
439. Bothriocephalus latus 561
440. Head of bothriocephalus latus 561
441. Proglottis of bothriocephalus latus 562
442. Eggs of bothriocephalus latus 562
443. Free embryo of bothriocephalus latus 562
444. Amœba coli mitis 563
445. Amœba dysenteriæ or coli felis 564
446. Balantidium (paramæcium) coli 565
447. Cercomonas intestinalis 565
448. Trichomonas vaginalis 565
449. Trichomonas intestinalis 565
450. Section through the wall of a bile-duct filled with coccidia 566
451. Coccidia from the bile-ducts 566
452. Development of spores in encysted coccidia 567
453. Epithelioma contagiosum 568
454. Parasites of epithelioma contagiosum 568
455. Miescher's sacs in various phases of development 569
456. Plasmodium malariæ of a febris quartana 571
457. Plasmodium malariæ of a febris tertiana 572
458. Plasmodium malariæ of a febris quotidiana 572

SECTION I.

Introduction.—Health and Disease.—Problems of General Pathology and Pathological Anatomy.

§ 1. WHEN the act of fecundation is completed, by the union of the spermatozoön with the germinal vesicle, there occur in the ovum a series of changes leading to the formation of a large number of cells, and finally to the production of an embryo, which, in the course of nine months [in the human species], reaches a definite stage of development, and is thereupon expelled from the maternal organism. When it is detached from the latter, its growth continues until completed after a series of years, the attainment of its physical maturity being followed by a long period of time in which the bodily weight remains approximately the same. After a number of years—the extent of time not going beyond a certain limit either in man or in the lower animals—the organism perishes.

In all Metazoa, in which the functions of the organism are allotted to certain cells and groups of cells, and in which, furthermore, the propagation of the species is dependent upon certain definite cells which are set loose from the maternal and paternal organisms, the parents invariably sink into death. For the maintenance of the species the individual has only this importance: it produces the germinal cells, and in the first stage of development harbors and nourishes them. Thus, if the offspring be freed from the maternal organs and be capable of existing without parental aid, the parents, if incapable of further production, have become superfluous for the maintenance of the species, and sooner or later cease to exist.

So long as the human organism lives, and is in a condition which we consider as one of **health**, its manifestations of life show a fixed character, and, within certain limits, are the same for all individuals. For example, the bodily temperature is nearly the same for all persons, and, notwithstanding the changes in the surrounding media, varies only to a slight degree. The number of heart-contractions in a minute is confined within certain limits, and, while differing somewhat according to age and sex, their frequency does not overstep certain boundary-lines for any length of time. The breathing is performed in a distinct rhythm. The ingestion of food, and its changes in the alimentary canal, are made up of a series of mechanical and chemical phenomena which are always repeated by the individual in the same way. The kidneys secrete a fluid which contains certain definite substances which are always of the same composition, and the chemical reactions going on in the body always reproduce themselves in the same way. Again, the nervous system, central and peripheral, with its end-apparatus, acts in a certain manner, which differs very little in different individuals.

The condition of the organism which we designate as **disease** is principally characterized by the fact that some function or functions of the organism are no longer carried out in the way which, from the fact that it occurs in all human beings, is considered as normal. One therefore recognizes disease in the greater or less number of changes in the manifestations of life, and disease is nothing else than **a life whose manifestations partly deviate from the normal.**

Nearly every function through which life manifests its relations to the external world — in the human organism, for instance, all the different and partly very complicated processes through which the organism accomplishes its nourishment, removes the products of nitrogenous metabolism from the tissues, and cares for the maintenance of the species — brings with itself also the manifestations of disease. The symptoms by which we determine that an individual is diseased are of a very manifold nature; thus it may happen that the functions of the organism are increased or diminished or destroyed, or they may in a greater or less degree deviate from the normal. It is, furthermore, very common, in a condition of illness, that at the same time not only one function, but many, may vary more or less from the normal, or even be entirely suspended. It is therefore necessary to have an extended experience, and it requires a thorough study, to enable us to recognize all the phenomena of disease and to diagnose correctly their meaning.

The **symptoms of disease** are partly **subjective** and partly **objective.** To the first group belong the feeling of uncomfortableness, debility, and sense of painful feeling in some particular part of the body or in numerous parts of the organism; dyspnœa, tightness of the chest, palpitation of the heart, loss of appetite, chills, fever, etc. — in short, a great number of phenomena which are referred partly to changes in single organs and tissues and partly to an ailing condition of the whole organism.

The objective symptoms, as well as the subjective, are partly local and partly general. The process of the digestion of food is often at fault; the contents of the bowel may be hurried along too rapidly, or may be retarded, or may not be discharged at all. The breathing is changed: at times slow, then hurried; at times shallow, then deep; over the lungs in these cases are not seldom heard abnormal sounds. The heart contractions are often quickened or slowed, strengthened or weakened, and often of an irregular nature; consequently the frequency and rhythm and quality of the pulse are changed. The sounds which are heard in the neighborhood of the heart may also be changed, or replaced or accompanied by new sounds. The urine often exhibits an abnormal appearance, and contains substances which are not normally found in it. In many forms of disease the sensitiveness of particular nerves is lowered, in others it is increased. In the muscles there is sometimes more or less paralysis; at other times involuntary contractions. In the central nervous system the greatest variety of disturbances of function may appear, determining conditions of excitation as well as those of depression or paralysis. Very often the bodily temperature, which normally only rises and falls within certain limits, is elevated, often very markedly, above the normal; and that condition which we designate as fever is mainly characterized by the increase of the proper warmth of the body.

The material substratum upon which the processes of a healthy life depend are the tissues of the body—that is, the cells and their derivatives, of which the tissues are composed.

Diseased life is connected with the same material substratum, and what we consider as **its symptoms** are **the life-manifestations of the tissues and of the organs of the human body.**

The function of a tissue is dependent upon the organization of its component parts. A kidney cannot perform any other function than the secretion of urine, and the constituents of the bile can only be separated by the liver-cells.

If the functions of any tissue manifest a change from the normal, it necessarily follows that **the organization of the tissue in question is changed.** Concerning the character of such changes experience alone gives an explanation, and experience has shown that in most cases these changes of the organization result in a *transformation of the physical make-up of the tissues*—that organs which have functionated in a pathological manner are changed to a degree that often enables us to recognize by even macroscopical examination numerous deviations from the normal appearance.

The number of observations which have been made in relation to tissue-changes in conditions of disease is already very considerable; and especially have the improved optical appliances which the last decade has brought to our aid greatly increased our knowledge in regard to the anatomical changes of diseased organs. Since most forms of disease in man show definite changes in the organs, when we speak of disease we now usually think not only of a group of symptoms, but rather of *a group of anatomical changes ;* our **conceptions of disease** have become materially **anatomical,** and we seek to know the character of a given disease by the investigation of the anatomical changes.

Still we are far from being able always to discern positively the corresponding changes of organization and structure of the tissue. Even in very severe and fatal diseases (as epilepsy, diabetes) there are times when no anatomical changes in any way commensurate with the phenomena observed during life can be proved; and numerous diseases are accompanied with functional disturbances the seat of which we are unable to locate with any certainty.

Nevertheless we may fairly assume in these cases also that the disturbed function is grounded on changes of organization. That we do not know what these changes are has its foundation in this: either that we do not look for them in the right place, or else that our optical aids are not sufficiently powerful to bring them to light. And even when histological changes are present we are often unable to recognize their pathological nature, from the fact that our knowledge concerning the nuclei and cells of the various tissues is not so far advanced as to enable us to distinguish in all cases that which is normal from that which is pathological.

It is difficult to say whether there exist any *purely functional* (dynamic) *disturbances*, in which the tissues suffer neither physical nor chemical changes. Provisionally we accept this in all cases in which we cannot give any better information. An example of such disturbances is seen in the toxic action of nerve-poisons, concerning which we cannot say in what way they exert upon the nerve-cells and nerve-trunks a stimulant or a paralytic effect.

The **causes of sickness** may be **external** or **internal.** *The former are dependent on the numerous injurious influences exerted by the external surroundings,* and can affect the organism as well in intra-uterine as in extra-uterine life. *The internal causes are the innate, springing from the embryonic alterations of the organization, or of any particular organ, or of several organs, and appearing either as spontaneous variations or as something inherited from progenitors.* If an organism be easily affected by a certain disease, we speak of it as being *predisposed* to that disease; if the reverse be true, we speak of it as being *immune.*

If a disease be entirely characterized by local symptoms, it is designated as a **local disease** or **disease of an organ**; when the organism appears diseased as a whole, one speaks of a **general disease**; should the morbid processes deviate for a long time from the normal, so that the whole organism seems to have become subject to essential changes, the condition is called a **constitutional disease.**

No definite separation, therefore, can be made between local and general diseases, for the reason that a disease may begin with local symptoms and, later on, lead to disturbances of the whole organism; conversely, a disease may begin with general phenomena, and disease of the organ follow.

This difference in the course of disease depends mainly on the different ways in which the deleterious influences of the external world act. If by such means only the tissues of an organ are damaged, local diseases occur. If, on the contrary, at the outset, changes of the blood and the fluids of the system appear, by means of which the function and the organization of numerous tissues are changed; if fever appear, and the nervous system be also affected, then the picture of a general disease is produced. If, still further, one organ be more seriously damaged than another, so that consequent disturbances of function are markedly apparent, then it will be proper to speak of the general disease as being accompanied by the symptoms of a local disease.

If an organ be attacked with disease, a **generalization of the disease** may occur from the spreading of the noxious agent by continuity and contiguity; also by its being conveyed in the blood and the other fluids of the body—either producing general disease or setting up in other organs the same condition of disease that was found in the organ first attacked. And furthermore, the changes in the functions of an organ may produce functional changes in another organ, or even, as a sequence, an ailing condition of the entire body. For instance, a chronic disturbance of the secretion of the kidney may produce a change in heart-function, and, later, poisoning of the whole body, including the nervous system, by means of the harmful products of metabolism, now no longer capable of being discharged from the body in the ordinary manner.

In many general diseases which begin with general symptoms we must assume that there was a primary lesion, this, however, being so mild as to produce only slight and circumscribed disturbances of function, and consequently no symptoms capable of being recognized. For example, it is in the highest degree probable that, in an infectious disease beginning with general phenomena, the poison causing the disease multiplies somewhere in the body, and at this point causes local tissue-changes and functional disturbances. Consequently even in this class of diseases it may be said that the morbid process has a local starting-point or several local seats.

Strictly speaking, even the so-called general and constitutional diseases are not really such, inasmuch as the tissues of the organism are practically never all involved in a diseased condition. The disease has, even in such cases, its local seats, but these are very numerous and are distributed over the greater portion of the body.

The **duration of disease** is very variable. A shock produced by a sudden fright, with the coexisting excitation of the vaso-motor nerves, is an instance of disease which may last but a few seconds. Tuberculosis, leprosy, and syphilis may give rise to sufferings lasting for years. Diseases characterized by a duration of a few weeks are called *acute;* those lasting for months or for a longer period are designated as *chronic.* Many diseases have a **typical course**—one which is repeated in every case without much variation; in others the course is markedly **irregular.** Some begin abruptly, others slowly.

The **termination of an illness** is either complete or incomplete **recovery,** or **death.** The first event is symptomatically marked by the return of the functions of the diseased organs little by little to their proper condition, until at last they do not deviate at all from the normal. In general diseases attended with fever the temperature sinks to the level of health, and the ailing condition of the body is transformed to one of well-being.

Ordinarily the return to health goes on without interruption, or at least without much deviation. Not infrequently, however, it happens that while the patient is convalescing the disease breaks out anew; in other words, there is a **relapse.**

The disappearance of the abnormal symptoms denotes a **restitution of the tissues.** The chemical processes of the body return to their normal state, the damage done to the cells is repaired, the dead cells being replaced by new ones of the same nature as the old, and the whole tissue is restored.

In many cases, after the disease has run its course, a complete restoration of the former condition of the tissues is produced. In severe sickness—that is, in severe tissue-lesions—complete anatomical restoration of the tissue is impossible; there will remain *defects* here and there, or *where a certain tissue is lost it may be replaced by another of a lower grade.* If in such cases, nevertheless, restoration of health ensues, so far as regards the functions, it is for the reason that the individual organs have a redundant amount of functionally capable tissue, so that the disappearance of a small group of cells is not appreciable. It therefore happens that, upon the destruction of certain parts, others do compensatory work, increase in size, and show a greater activity of functional power.

Thus there will be permanent disturbances of function only when the diseased organ has not enough healthy tissue to carry on the work and other organs are not capable of acting as a substitute for it, or as compensatory to it, or if the disease leaves such changes as to produce permanent disturbances of function in the same organ or in another organ having similar functional capacity.

We must regard it as an incomplete convalescence when, although the symptoms of the disease have disappeared, the harmful influence which caused the trouble is not destroyed, but remains in the body, with the possibility that sooner or later the disease will break out anew. Strictly speaking, we have not a cure, but only the **latency of the disease process.** This condition occurs most frequently in the chronic infectious diseases.

Upon the **occurrence of death** all functions of the organism cease.

The order in which the various organs of the body suspend and annul their functions varies, in accordance with the nature of the disease. The death of the individual is absolutely determined when the functions of the heart and brain are definitively inoperative.

Through the victory of an organism over a disease the body not seldom becomes immune against the particular poison which caused the disease from which it has recovered. Often, however, on the contrary, the body, during the course of a disease, or during convalescence from it and after its disappearance, is *predisposed to certain other diseases.*

§ 2. The **scientific investigation of diseased life** may reach its conclusions from the symptoms of a disease, and practical medicine is markedly concerned in learning the meaning of morbid phenomena in each individual case observed by the physician. The exact investigation of pathological symptoms chiefly serves the purpose of determining the different forms of disease present in given cases, and of separating one disease from another; at the same time it should also furnish us with the power of penetrating into the origin of the different phenomena, and of determining their connection with the changes in the organs and tissues. So far as an investigation of disease symptoms at the sick-bed serves useful diagnostic and therapeutic purposes, it belongs to the domain of *practical medicine* and of *special pathology*, the object of which is to learn to know the phenomena, as well as the course and termination, of the individual diseases, and to find means of controlling them. If the investigation is mainly concerned in determining the nature and the origin of disease phenomena, without regard to their assignment to special forms of disease, it falls within the scope of **general pathology,** *which has for its object the acquisition of definite data concerning the nature and course of disease processes.*

Various authors, in seeking to define the field of general pathology, have sought its problems in different directions, and their arrangement of its proper constituent elements is not always confined within the same boundaries. If one faces the task without regard to its practical bearing on the subdivision of science (specialism), it inevitably follows that general pathology must be held to deal not only with the theory of the nature and the course of disease processes, but also with their causes; that it not only embraces that section of natural science which we call **pathological physiology,** but includes at the same time the **theory of the causes and nature of disease.**

As the morbid symptoms are neither more nor less than biological manifestations of pathologically changed tissues, so the **theory of disease changes of the tissues,** or **general pathological anatomy,** naturally falls into the domain of general pathology.

The great extent of the field embraced by general pathology, both in text-books and in the lecture courses, would make it appear reasonable that the limits of a course in general pathology should be narrowed, and that special portions of it should be relegated to the special departments to which they belong.

Notwithstanding that the theory of the symptoms of disease forms the largest portion of general pathology, it seems to be expedient to leave to special works, to lectures, and to preparatory instruction those facts which are perfected at the bedside and are readily capable of utilization for directly practical purposes.

General pathology must also undergo a further contraction in the field of the study of the causes of disease, because the latter are purposely brought within the circle of consideration only so far as pathological changes are really caused through them, while the further and more extended relations to the outer world in which we find ourselves—relations which eventually can produce harmful influences upon our organism—are to be turned over to *hygiene*.

The main point of interest in general pathology lies indisputably in the **knowledge of the anatomical changes which are at the bottom of the disease processes.** But the studies in this domain do not need to be confined to the effort to ascertain the morphological characteristics of disease processes; they should rather penetrate into the questions of *how these processes are brought into existence and what is their nature.* A scientific treatment of pathological anatomy, therefore, leads necessarily also to the study of the **etiology** and the **genesis of the disease processes.** If by the study of etiology we are able to prove the cause and development of the changes induced by disease, then shall we also be able to gain an understanding of the phenomena of disease as they come under observation during life, and also at the same time to lay the foundations for an adequate knowledge of that part of general pathology which is designated by the term **pathological physiology.**

SECTION II.

Cause, Origin, and Course of Diseases; General Considerations.

I. Origin of Diseases through External Pathological Influences.

1. *Origin of Diseases through Deficiency of Food and of Oxygen; by Fatigue; by Heat and Cold; by Changes of the Atmospheric Pressure; by Electrical and by Mechanical Influences.*

§ 3. FROM birth until death man is continually subject to the influences of the surrounding external world, some of which influences aid, while others hinder, the exercise of his functions.

As long as the human body is able to utilize its functions for the purpose of spontaneous changes of relation to the external world, and also to accommodate its functions to the external necessities of life, so long does it remain in health. If its contrivances of adjustment are no longer able to neutralize surrounding influences, and man can neither escape nor change the necessities of life, he falls into sickness or dies.

For its preservation the body requires first of all a certain amount of nutrient material, as well as a definite quantity of water and of oxygen; and while man is able to survive the loss of these agents for a short time, yet, beyond a certain degree and after a limited time, **insufficiency of oxygen, food, and water** must necessarily occasion sickness or death.

The **suppression or diminution of the supply of oxygen** to the tissues is an occurrence that can happen at all ages, and may be due either to a lack of oxygen in the surrounding medium, or to a hindrance in the transportation of the oxygen contained in the air to the lungs and the blood, or, finally, to an inability of the blood to take up the oxygen in sufficient quantity. Lack of oxygen can occur to the fœtus within the uterus, through the mother herself suffering from want of oxygen, or through premature separation of the placenta, or by means of disease changes in the placenta, or through compression of the cord, the gaseous interchange between the blood of the mother and of the fœtus being thereby hindered. After birth an insufficient supply of oxygen can happen through hindrances occurring to the breathing-power of the lungs, or through the fact that the child itself is too weak to sufficiently expand the thorax, in order to introduce sufficient air, by means of the respiratory movements of the lungs.

If the supply of oxygen be stopped completely, either through any fluid—e.g., water—getting into the respiratory tract in place of air, or from the air-passages being closed, the individual thus affected dies in a short time from lack of oxygen, by "**choking**" or **suffocation.** If animals remain in a closed place for a certain length of time, death is found to occur as soon as the oxygen of the air reaches 2 or 3 per cent. by volume, it being normally 20.8 per cent. by volume (Cl. Bernard, P. Bert).

If the supply of oxygen be not entirely arrested, but only markedly diminished in amount—as may occur in carbon-dioxide poisoning, where the firm combination of carbon-dioxide gas with the hæmoglobin prevents the taking up of the oxygen by the blood-corpuscles—suffocation follows only after the lapse of several days. By the gradually increased shutting off of the supply of oxygen, and accumulation of carbon dioxide in the blood—as in cases of narrowing of the lumen of the larynx by inflammatory exudations and through compression of the windpipe from goître—there occur breathlessness, cyanosis, cramps, and disturbances of consciousness, a condition which we call **asphyxia.**

If the supply of oxygen be diminished even in a small degree, but for a long time—a condition which may occur, for example, in a diminution of the blood-cells in oligocythæmia—there will take place in the tissues of the organism degenerative processes which are characterized by an increase of the destruction of albumin, and by fatty changes in the organs (Fränkel), and may cause not only disease, but ultimately death.

If the body be **deprived of all nourishment and water,** then, as albumin and fat still continue to undergo decomposition, a rapid diminution in the body-weight occurs, and finally death ensues. According to Lehmann, Müller, Munk, Senator, and Zuntz, the total amount of oxidation does not go below the amount which would be observed in the same individual under favorable circumstances and when in a normal condition. There takes place a marked conversion of albumin into other products, as well as a decided loss of water. In animals death follows when about 40 per cent. of the body-weight has been lost, nearly half the deficiency being due to a diminution in the muscles.

Fat disappears the most rapidly, and may be reduced even to 93 per cent. of the entire amount originally present. The diminution of substance takes place in the various parts of the organism according to the following order: liver, spleen, testicles, muscles, blood, alimentary tract, skin, kidneys, and lungs. The heart, the nervous system, and the bones show the least loss of weight, although the investigations of Lehmann, Müller, Munk, Senator, and Zuntz have shown that an absorption of the bony tissue takes place during starvation, and if water be ingested an increased amount of phosphoric acid and calcium is found to occur in the urine. In the blood the white corpuscles diminish rapidly in number (Luciani); the red blood-cells may, on the contrary, in a given quantity of blood, be increased. According to the investigations of Coën, the organs of starved animals plainly exhibit the evidences of vascular engorgement, with here and there hæmorrhages, and also inflammatory changes, as, for instance, in the intestines, the liver, and the kidneys.

In the nervous system no special changes have been noted (Peri).

The fatal issue in the case of absolute withdrawal of nourishment and water occurs in man in from seven to twelve days, under certain circumstances; according to some authors, only after twenty to thirty days; bodily exercise hastens the fatal termination. This period is considerably extended if water be taken into the system. In this case there is found an increase in the nitrogenous constituents of the urine.

Life can be maintained for a long time with insufficient nourishment; there occurs, however, a certain diminution of bodily weight, which may under certain circumstances lead to the most marked emaciation, and finally to death. The same thing happens when the composition of the food is unsuitable, and only a portion of the nutrient material is offered in sufficient quantity, so that the body is starved in albumin, or in fats, or in salts, or in water. Dogs deprived of all nitrogenous nourishment die in from thirty-one to thirty-four days (Magendie). If the nourishment be sufficient, but poor in albumin, there occur, after a certain length of time (in dogs after six weeks), loss of appetite and an unwillingness to take the proffered food, and digestion and assimilation in the animal are lessened (Munk). Especially is this the case if the nourishment be deprived of fat, while it holds to a lesser degree if the aliment be wanting in albumin and carbohydrates. Very likely this deficiency of absorption is chiefly dependent upon a diminution of the secretions of the digestive juices, this being especially noticeable in the bile. The excrement at last is found to be nearly without bile.

§ 4. If the **functional activity** of an organ **be exerted for a considerably longer time than that to which it is accustomed**, there will occur, sooner or later, a state of exhaustion, due in part to the consumption of the parenchyma of the organ, and in part to the formation of toxic nitrogenous products of metabolism, these making such an organ unfit for further continued action. If this exhaustion affects a vital organ, such as the heart, death may ensue from this cause alone. This result can take place, however, as well when the heart is unable to perform its ordinary function for a short time as when it acts a long time more nearly normally, indeed, but still under the conditions demanded of a maximum amount of work. If the wearied tissues are able to secure rest, and if a sufficient and proper amount of nourishment be supplied to them, the extra material which was lost by the unusual activity will be again replaced, the effete products of metabolism which are acting detrimentally to the functions of the tissue will be removed, and the part will again become ready for a renewal of its normal activity.

If a tissue frequently becomes the seat of exhaustive functional activity, and the periods of rest are too short to admit of a complete restoration of the tissue, there will finally occur a condition of permanent insufficiency, a chronic exhaustion, which under certain circumstances may even lead to degeneration or atrophy of the affected organ. A gland or a muscle may thus become atrophied through excessive use, and a brain which, by too constant stimulation of any character without the required periods of rest, is exhausted by its continuous activity, may finally pass into such a condition of debility and exhaustion as to make even the performance of the normal function an impossibility. By means of rest and of regulated nourishment the brain may again recover; in a high degree of exhaustion, however, the functional insufficiency may become permanent, and may find its expression eventually in anatomical changes.

If the excitation of the nervous system be very severe, there occurs under certain circumstances, by even a short continuation of the source of the irritation, a cessation of the nervous functions—a paralysis which, should it affect the functional capacity of the heart and the respiration, may lead to death; more often, however, it passes away after a short time.

In organs from which much work is required, exhaustion and insufficiency take place so much the more quickly in proportion as the nourishment is insufficient. Fatigue and insufficiency of the heart are most often observed when the general nourishment is poorest, as from disease of a febrile character, or when the absorption of oxygen in the blood is more or less hindered by heart-defects poorly compensated for and by diseases of the lung.

If the demands upon a muscle or a gland are only slightly increased, and if at the same time the nourishing material be good and sufficient for the carrying out of such increased work, the **affected tissue becomes hypertrophied** and is thereby rendered capable of accomplishing the increased work for a time.

§ 5. **High temperatures** act in part by a *local destruction of the tissue* (burning), in part by an *overheating of the entire body.* Naturally the latter condition is only possible when the high temperature acts for a length of time sufficient to render it impossible for the organism to protect itself from the excess of temperature by giving up its heat. In dry air of 55–60° C. (131–140° F.) even the most profuse perspiration is no longer able to hinder the body from becoming overheated, and in moist air even a lower temperature suffices.

If a rabbit is placed in an incubator at 36° C. (96.5° F.), its temperature rises up to 41–42° C. (105.8–107.6° F.). At the same time the respiration and the pulse are accelerated, and the superficial vessels become dilated. At about 40° C. (104° F.) the body-temperature is elevated to 44–45° C. (111.2–113.° F.), and the acceleration of the breathing and of the contractions of the heart is enormous; the pupils become dilated, and the muscles are relaxed. After a time death ensues through paralysis of the nervous and contractile systems, especially through failure of the heart. As the muscular substance of a mammiferous animal coagulates at 44–45° C. (Kühne), it follows that, by such excessive heating, death may result from coagulation of the heart and respiratory muscles. Continuous inclosure for several days in an incubator is fatal to animals even though the body-temperature does not exceed 42° C. (107.6° F.). The destruction of albumin is increased by the elevation of the body-temperature, while at the same time the elimination of carbonic-acid gas is diminished (Naunyn). In many of the tissues fatty changes occur.

If a man is subjected to a high temperature, an overheating of the body may take place, and finally the condition may occur which is designated by the name of **heat-stroke.** In this condition the pulse is increased, the respiration is rendered galloping and panting, the pupils are dilated, and death may take place in the same manner as in the case of an animal made the subject of experiment. The occurrence of the heat-stroke is hastened by severe bodily labor, by interference with heat-dissipation, by impermeable clothing, or by lack of water in the body. By direct action of the rays of the sun upon the head cerebral and meningeal symptoms may be produced. This condition is characterized by hyperæmia and inflammatory exudations, and is called **sunstroke** or **insolation.**

Local effects of heat upon the skin (**burns**), according to the time during which their action is exerted, and according to the intensity of the heat, lead to hyperæmia (first degree of a burn), or to the formation of blebs (second degree), or to tissue-eschars (third degree), or to carbonization (fourth degree). The action on the tissues depends upon the heat—first locally and then more extensively,—and their destruction results from a certain degree of temperature acting for a certain length of time.

If a large part of the surface of the body, about one third, is burned, the individual dies, even though the burning is only of a mild character and eschar-formation does not take place. An attempt has been made to explain this phenomenon in various ways. Billroth, Foà, Mendel, and others believed the cause of death to lie in the suppression of perspiration and the consequent collection of poisonous materials in the blood; others, as Sonnenburg and Falk, believed the fatal result to be due to a reflex lowering of the vascular tone. In marked cases, according to Sonnenburg, the overheating of the blood causes paralysis of the heart. On the other hand, Ponfick, Klebs, von Lesser, and others consider the fatal outcome to be chiefly due to injury and destruction of the red blood-cells. Silbermann, Welti, and Salvioli also seek the cause of death in injury to the blood, laying especial stress, however, not so much upon the destruction of the red blood-cells as upon the occurrence of stasis and coagulation of blood within the vessels of the different organs, this condition being the consequence of the injury to the blood. Kijanitzin, on the contrary, holds that a poison (ptomaïne) which acts detrimentally to the organism, is created in the bodies of those who have been burned.

The anatomical findings in those cases of burns in which an opportunity has been given for examination tend to demonstrate that—in cases in which death does not follow in a short time from the severe disturbance of the nervous system and the overheating of the body—the cause of death occurring from burns of the cutaneous surface is to be sought in the changes of the blood and in disturbance of the circulation. The blood-changes consist in destruction of the red blood-cells, or such an injury to them as to diminish their functions and give rise at the same time to the deposit of the products of degeneration and the collection of hæmoglobin in the liver, the spleen, and the kidneys. The alterations are further characterized by a tendency of the blood to form thrombi and intravascular clots, by means of which vessels of the lesser as well as of the greater systemic circulation may be obstructed. And besides these should be mentioned the facts that both during life and after death venous clotting and hæmorrhages, as well as arterial anæmia, are occasionally observed, and that local tissue-degeneration and necroses may occur in certain organs, as, for example, in the kidney, the liver, and the gastric and intestinal mucous membrane, in bones, and in the soft parts.

Low temperatures act in much the same manner as do high temperatures, in part through local injuries and death of the tissues, in part by chilling of the entire body. Severe and lasting refrigeration causes tissue-death; after mild chilling there occur, as a consequence, tissue-changes, such as hyperæmia and exudations which are exceedingly rich in leucocytes. The tips of the nose and of the ears freeze the easiest, as in these localities the warming of the tissue by means of the circulating blood becomes soonest insufficient.

If the entire body be strongly cooled, a condition of general paralysis finally occurs, through reduction of the normal excitability of the tissues, especially of the nervous system and of the heart. The sensorium is dulled; the heart-contraction and respiration become progressively weaker, and finally cease entirely. If, before the excitability of the tissues has entirely disappeared, the body be again warmed, the power of movement in the limbs returns gradually, and, after a certain time, consciousness is restored. In man, refrigeration of the body to 24–30° C. (75–86° F.) has been observed, ending in complete recovery. According to Ansiaux, the rectal temperature of animals from which heat has been abstracted may amount to 14–28° C. (57.3–82.4° F.) before death ensues.

Besides the severe forms of local or general lowering of the tissue-temperature, there also occur, as harmful pathogenic influences, mild general or local chillings—the so-called "**colds**"—from the effects of which disease phenomena manifest themselves, partly at the seat of refrigeration and partly in other organs in distant portions of the body. For example, after widely extended refrigeration of the skin may result diarrhœa, or catarrh of the respiratory system, or kidney-disease; after local chilling of the skin, painful affections in the deeply seated muscles. In what manner the phenomena referred to depend upon the refrigeration is unknown, but there is no reason to deny that these manifestations of disease are caused by cold. But though many diseases formerly attributed to "catching cold" have been found to be due to infectious diseases, there still remain a number of diseased conditions for which we know no other etiology than that of refrigeration. Conditions of the body in which the skin is hyperæmic and in which perspiration is secreted seem to favor the attacks of disease caused by cold. In many individuals there seems to be a special disposition for the effects of refrigeration to manifest themselves in connection with definite tissues, so that in one person certain muscles, and in another the mucous membranes, will be the parts affected.

According to Pflüger and others, the processes of life in animals may be brought to a standstill by means of the abstraction of heat, without its being an impossibility for an awakening to take place from apparent death. This is said to happen, indeed, if an animal be frozen to a solid mass. Preyer is also of the opinion that the continuity of life can be fully interrupted by refrigeration, and describes the subjects who are thus "lifeless," but still capable of living, as *anabiotic*. Frogs are said to remain vital for many hours, even though the temperature be reduced to −2.5° C., at which temperature the heart is frozen. On the contrary, Koch could not observe such anabiosis in fully frozen animals, such as fishes, beetles, or frogs; these were able to endure refrigeration under the freezing-point only when the time of the influence was insufficient to solidify the internal parts of the organism.

Tissues of mammals and of man do not necessarily succumb to the abstraction of heat, if it be of short duration, even though the freezing-point be reached, but may again recover.

§ 6. Sudden **lowering of the atmospheric pressure,** as occurs in the ascension of mountains and in balloon voyages, can cause conditions of great exhaustion, with marked palpitation of the heart, unconsciousness, irregular breathing, and sometimes vomiting and hæmorrhages from the gums and lips. Probably these phenomena depend chiefly upon lack of oxygen (P. Bert), the capillaries of the lung being unable to take up sufficient oxygen from the strongly rarefied air. Owing to the demands made upon the muscles in climbing a mountain, these phenomena appear at a less elevation than in a balloon ascension. Hæmorrhages are probably due in part to the occurrence of fissures, through drying of the mucous membrane of the parts affected by evaporation (Hoppe-Seyler, von Recklinghausen).

According to the researches of Egger, Miescher, and others, a sojourn in high altitudes causes an increase in the number of red blood-cells in a short time, with an augmentation of the amount of hæmoglobin in the blood. Upon the return to the lowland, the increase in the number of the red blood-cells disappears.

Sojourn in diving-bells and caissons—such as are used for carrying on building operations beneath the water—in which, under certain circumstances, the **atmospheric pressure is increased** to more than four atmospheres, causes a trifling difficulty in respiration and slight acceleration of the circulation. Upon going quickly from the compressed air to the open air there may occur fatigue, a sense of oppression in the chest, noises in the ear, cramps in the muscles, pains in the joints, hæmorrhages from the nose, ears, and lungs, dilatation of the pupils, and, under certain conditions, paralysis, coma, delirium, and even death after an interval of from one to twenty days. The cause of these phenomena is probably the sudden escape from the blood of the nitrogen which had been absorbed under pressure (P. Bert, Hoppe-Seyler). According to the investigations of Leyden and Nikiforoff, degenerated areas are observed in the white columns of the spinal cord in the fatal cases associated with paralysis. In these areas of degeneration some of the individual nerve-fibres are torn apart, and, by the swelling of the axis-cylinders and the disintegration of the medullary sheaths, the tissue is markedly changed, empty spaces taking the place of the nerve-filaments. Probably these disturbances are incident to the formation of bubbles of gas inside the spinal cord. If the gray matter is affected, the ganglionic cells may also degenerate.

Changes in the electrical condition of the atmosphere and in the magnetism of the earth have no demonstrable influence upon the body of man; on the other hand, **electric discharges**, as lightning-stroke, induce in part local burning (Fig. 1) and in part lesions of the whole body. Under certain circumstances lightning-stroke can cause laceration of the tissues of the internal organs, as of the liver and of the heart (Liman). The most frequent and important action of lightning is to cause a *paralysis of the nervous system* which gives rise to severe dyspnœa, sooner or later ending in death, or gradually passing away. Only very rarely do the special nerves remain lastingly affected. Transitory paralyses occur when the lightning has not passed through the body, but has only been conducted in its neighborhood, whereby, in consequence of the sudden electrical discharge from the clouds, the body of the affected individual is quickly emptied of its electricity, or else the electricity present in the body is combined with the electricity discharged from the clouds.

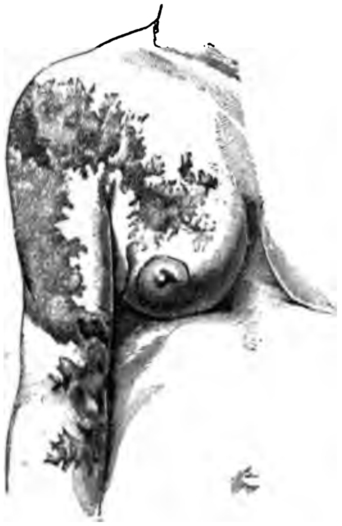

FIG. 1.—Lightning-figures on the shoulder, breast, and arm of a woman struck with lightning.

Individuals who have been struck by lightning show mild or severe burns at the points of entrance and exit, as well as destruction of the tissues in the path of the bolt. The marks of the burn are mostly red, forming peculiar ramified, zigzag lines, the so-called *lightning-figures* (Fig. 1), which are essentially a hyperæmia, and soon disappear if severe burning has not occurred.

Mechanical influences are frequently productive of pathological conditions, causing those lesions which are known as contusions, wounds, lacerations, fractures, concussions, etc. These influences act through destruction of tissue, through changes in the organization of tissue, not externally recognizable, through lesions and ruptures of the vessels, and through irritation of the nerves. The sequelæ are destruction of tissue, disturbances of the circulation, inflammations, and growths due to proliferative processes. Frequently repeated, though trifling, mechanical traumatisms, as rubbing, cause congestive hyperæmia followed by inflammation and, if the traumatisms are continued, hyperplasia of the tissues. If large quantities of insoluble dust-particles are continuously brought to the lungs, marked changes will be noticed in the lungs themselves and, under certain circumstances, in other internal organs. One can group these changes under the name of **dust-diseases.** Continuous pressure and diminution of the amount of space allowed an organ may cause atrophy of that organ, as seen in constricted liver following tight lacing.

§ 7. Mechanical, thermal, electrical, and many chemical agents, especially those of a corrosive nature, cause: first, local injuries to those tissues which may be attacked directly; second, a *general involvement of the nervous system through the influence of the local irritation.* The trauma can produce this involvement by directly attacking the central nervous system or through the irritation of the sensory or sympathetic nerves, thus producing a number of additional nervous symptoms.

If the cerebral functions are disturbed by direct agitation of the cranial contents, and unconsciousness is the result, the condition is termed **commotio cerebri** or **concussion of the brain.** This term is given, however, when the trauma has not visibly altered the structure of the brain, at least not to a considerable extent nor in a striking manner.

Should phenomena of inhibition and paresis be produced reflexly by intense irritation of the peripheral nervous system, especially attacking the functions of the heart and the respiratory tract, the term **shock** is commonly employed to designate the entire group of symptoms observed under these conditions. The most common causes of shock are injuries to the vertebral column, abdominal cavity, or scrotum; less frequently to the extremities or to the thorax. Further, shock is caused by lightning, burns, corrosions of the skin, fear, and psychical emotions, through whatever channels they are conveyed to the brain. An individual whose nervous system is in a particularly irritable condition is especially liable to shock; conditions of alcoholic or drug narcosis inhibit its appearance.

Shock is chiefly characterized by weakened energy of the heart's action; by an irregular breathing, which leads to a decrease in the interchange of gases in the tissues; and by a lowering of the temperature (Roger). Owing to these conditions the venous blood of persons dying from shock is lighter in color than the normal venous blood (Roger). In shock consciousness generally remains, the skin and the visible mucous membranes are pale, and the pulse is small and markedly slowed, often being irregular and interrupted.

In a person suffering from shock the nervous symptoms are varied. He may be agitated, and groan, shriek, and cry out with fear. This anguish of mind is associated with full breathing, and is known as *erethistic shock*. He may lie quiet, partially conscious, with sunken countenance, showing evidences of marked weakness in the sensory and motor functions. This combination of symptoms is known as *torpid shock*. In severe cases death follows from the stopping of the heart's action and the cessation of the respiration.

Shock, in its irritation of the terminal fibres of the peripheral nervous system, is closely allied etiologically to that phenomenon which we call **syncope.** Syncope, however, is to be differentiated from shock in that the chief symptom is a loss of consciousness of short duration, while the heart's action and the breathing show no marked disturbance. In syncope we have prodromes, such as giddiness, tinnitus aurium, and darkening of the visual fields, all of which are absent in shock.

Not infrequently, as the result of injuries in various portions of the body, there may arise more or less marked functional changes in the nervous system, which often remain after the local injuries to the tissues are entirely healed. These changes cannot be considered in any way dependent upon anatomical changes of the peripheral or central nervous system, but must be considered as *purely functional alterations of a psychical origin.* They are generally termed **traumatic neuroses, nervous diseases of accidental origin,** and are frequently characterized by subjective, but sometimes also by objective symptoms. To the first class of symptoms belong pains which are not necessarily localized at the seat of the injury, as, for instance, headache, chest-pains, backache, difficulty in motion, general lassitude and inability to perform mental labor, dulness of perception, disturbed vision, flittings before the eyes, giddiness, restless sleep, loss of appetite, and indigestion. To these symptoms Oppenheim and Strümpell have added psychical ill humor of a hypochondriac or melancholic character, irregularly placed patches of cutaneous anæsthesia, enfeeblement of sense of taste, hearing, or smell, motor palsies, hyperæsthesias, concentric narrowing of the visual fields, pareses, muscular spasms, tremors, acceleration of the pulse, and a tendency to sweating.

According to the opinion of the writers upon this subject, we are dealing in these cases principally with symptoms which are referable to a psychical shattering of the perceptive life, a psychoneurosis, which is less often caused by the traumatism and the accompanying psychical shock than by the consequent anxiety over the injury to health and loss of business. Sometimes, through disturbance of the normal relation between the mental processes, the patient's condition is changed to one that suggests hysteria, in part due to the spontaneous occurrence of abnormal sensations, called hypochondria, and in part to a neurasthenia. If volition no longer finds a way to the motor centers, hysterical palsies are established. If the normal exertion and inhibition of the will-power be broken down, so that unreasonable will-stimuli are created and reach the muscles, we have hysterical convulsions, contractures, or cramps. If the nervous irritation originating in the sensory tract does not enter the area of consciousness, we have an hysterical anæsthesia. If there are present in the consciousness images of awaited or feared objects, and if these images be intensified by the conditions of the disease into true subjective irritations of consciousness, we shall have hysterical pains and neuralgias (Strümpell).

2. *The Origin of Diseases through Intoxication.*

§ 8. *By* **poisoning** *or* **intoxication** *we mean that impairment of health, occasioned by the injury to a tissue of the body, which certain agents are capable of producing, under suitable circumstances, by reason of their chemical nature.* Those substances which are designated as **poisons** belong in part to the mineral, in part to the vegetable, and in part to the animal kingdom. Poisons are found as such in nature, or are produced artificially from organic or inorganic substances, which either may be non-poisonous themselves or may possess properties quite different from such poisons. Among the most important poisons are the products of the metabolism of animals or plants. The combinations which take place under these circumstances are formed either within the tissues of the plant or animal, or from the nutrient materials surrounding them, through the occurrence of transformations of non-poisonous elements, or of elements which exert an entirely different action.

The *poisons which belong to the mineral kingdom or which are produced from minerals* are: metallic mercury, chlorine, bromine, iodine, sulphur, and various combinations of these substances, besides many combinations of arsenic, antimony, lead, barium, iron, copper, silver, zinc, potassium, sodium, chromium, etc. The best-known poisons containing carbon which are artificially produced are: chloroform, chloral hydrate, ether, alcohol, iodoform, carbon disulphide, hydrocyanic acid, potassium cyanide, oxalic acid, nitroglycerin, nitrite of amyl, petroleum, carbolic acid, nitrobenzol, picric acid, and aniline. In general it is to be noted that modern chemistry is continually producing new substances which act as poisons.

Among the *poisons produced by plants of the higher order*, which are especially noteworthy, are: the *organic alkaloids*, such as morphine, quinine, colchicine, atropin, hyoscyamine, veratrine, strychnine, curarine, solanine, nicotine, digitalin, santonin, aconitin, cocaine, coniine, muscarine, and ergotine, all of which may cause severe poisoning, even in small doses.

Lower forms of plant life, especially the bacteria, produce non-poisonous and poisonous substances in the nutrient material (albuminous bodies) *in which they develop.* Some of these substances are similar to the vegetable alkaloids, some to the ferments, and are accordingly termed *toxic cadaveric alkaloids*, *toxic ptomaïnes*, *toxins*, *toxalbumins*, and *toxenzyms* (compare § 12; also Section IX.). It follows that the blood, the flesh, or any organ of a healthy animal may acquire poisonous properties, in consequence of changes which are set up in them by the influence of bacteria. Those diseases which are held to be due to sausage-, meat-, fish-, and cheese-poisonings are in part ascribable to the fact that bacteria have developed in these food-products, and out of albuminous material have produced the poisonous products of metabolism. In other cases the bacteria may have developed in the slaughtered animal during its life, so that the animal was diseased when killed; and the person eating its flesh acquires the poison, or is infected by the identical disease with which the animal was affected. Under certain conditions food which is in no way spoiled, but which contains bacteria, may be taken into the stomach and digested, and the bacteria thus liberated may develop in the alimentary tract of man and produce poisoning, by means of the toxins, toxalbumins, or enzyms which are formed by their multiplication.

Among the *animals which normally produce poisons within certain tissues of their bodies* the best known are: serpents, toads, salamanders, scorpions, Spanish flies, and many other insects which are supplied with stings. Latterly much attention has been given to the poisonous substances which are to be found in the internal organs of fishes and mollusks. There are certain forms of sea-fish that are constantly poisonous, and others also that are only poisonous at certain times; such observations have been made especially on the fish in Japanese waters. According to Saotschenko, the poison in many poisonous fishes is secreted by the glands of the skin at the roots of the dorsal and caudal fins, and may be found in their eggs. According to Remy, Miura, and Takesaki, the poisonous fish belonging to the family Gymnodontes (tetrodons) secrete poison only in the sexual organs. According to Mosso, there is found in the blood-serum of eels a poisonous substance, ichthyotoxin, which acts detrimentally if ingested into the intestines of the ordinary animals used for experimentation, and can produce death. Observations of poisoning from eating mollusks have been recently made at Wilhelmshafen which have excited considerable interest. Severe illness, with death in certain cases, followed the eating of moss-mussels (*Mytilus edulis*).

According to M. Wolff, the poison is contained in the liver of the mussels. According to Schmidtmann, Virchow, Salkowski, and Brieger, the action of the poison is similar to that of curari. According to Brieger, there can be obtained from the poisonous moss-mussels basic substances which are similar in their composition to the ptomaïnes—that is, to the basic products of decomposition. How far the causes of the poisoning are to be ascribed to normal and how far to diseased processes in the life of these fishes and mollusks has not been determined at the present time. From the fact that the moss-mussels were only poisonous in certain areas (Schmidtmann, Wolff) where the water was impure, and that the starfish found in the same localities were similarly affected (Wolff), it would seem probable that in a certain number of cases the poisonous action observed in the mussels, as well as in the starfish, must be referred to the influence of uncleanliness, or to pathological alterations of the natural processes of life. It is probable that the bacteria which are found in mussels which live in stagnant canal-water may be the cause of the deadly action (Lustig). In other cases the cause seems to have been connected directly with special circumstances; for instance, with the production of elements elaborated by the sexual organs.

It is difficult to give an exact definition of a poison and of poisoning, since the action of the substances considered above varies with the dose and the attenuation, as well as with the method of introduction into the tissues of the body. It is well known that even the most powerful poisons may be introduced into the tissues in small doses not only without doing damage, but even in such a manner as to produce a beneficial and curative effect upon them. On the other hand, substances which are not usually classed among the poisons, as, for instance, non-corrosive sodium salts, when introduced into the organism in large quantities or in concentrated solutions, induce phenomena which must be ascribed to the action of a poison. Furthermore, poisonous substances sufficiently diluted (phenol) may serve as foods. In the above definition I have come to the same conclusion as Kobert, and have utilized in the following paragraphs, concerning the workings of poisons, much material from his "Text-book on Intoxications," published in 1893. In this work a very large and rich amount of material is gathered together and well summarized.

§ 9. **Poisons** may be divided according to their action into three classes: first, those which produce local changes in the tissues; second, those which produce an injurious action upon the blood; third, those which produce in the tissues anatomical alterations which are not recognizable.

The **poisons which produce pronounced local alterations in structure** injure primarily the tissues with which they come directly in contact upon entering the body. If these substances are absorbed by the juices of the body, injury may result to the most diverse organs and tissues; but they most frequently confine their action to the organ in which they are stored up, or to which they are brought for purposes of secretion, as, for instance, the liver, the intestines, or the kidneys.

The most frequent situation for the primary injurious action is the mucous membrane of the upper alimentary canal and the respiratory tract; but in many cases of poisoning the skin is the first point attacked. Very often poisons are employed as disinfectants—i.e., they are purposely used to prevent the growth of or to kill off bacteria which have come in contact with wounds. When thus used they can produce local changes in the tissues, or, through absorption by the circulatory streams, injure the internal organs or the entire body.

The first group of poisons to be discussed here is made up of those substances which produce severe changes in the tissues at the point of contact. From the similarity of the results of this contact to burns, these poisons have been called **caustics,** or **corrosive agents.** If the action of the caustic reaches the highest characteristic grade, the tissue attacked will be entirely destroyed, in one case being converted into a dry, hard crust, in another case into a moist, soft one. If the action is less severe—because of the application of a less concentrated solution of the caustic, or because the chemical substance, though applied in concentrated solution, acts incompletely, or because the tissue itself is resistant, as in the case of the skin—we have less severe changes, which are characterized by redness, swelling, inflammation, and hæmorrhages. Very often one finds in the same organ diverse changes, as local sloughings or necroses, hæmorrhages, inflammations, and swellings due to slight local extravasations of blood. If the condition has been present for some time, the local changes are more or less wide-spread, while in a single application of the caustic the tissues are inflamed only within a limited area.

As substances which act in this manner should be mentioned the *corrosive acids:* sulphuric, nitric, hydrochloric, phosphoric, oxalic, acetic, arsenious, arsenic, osmic, lactic, carbolic, and salicylic. To this class also belong the *corrosive compounds of the alkalis and alkaline earths,* as potassium and sodium hydrate (watery solutions of KOH and NaOH), caustic ammonia (NH_3 dissolved in water), ammonium carbonate, caustic lime, and barium sulphate. To this list should also be added a number of corrosive salts, as those of antimony (tartar emetic and antimony trichloride), salts of mercury (corrosive sublimate and red precipitate), nitrate of silver, chloride of zinc, sulphate of zinc, sulphate of copper and acetate of copper, aluminium acetate, potassium chromate, potassium bichromate, and chloride of iron.

Among the especially irritant *poisons derived from animals* are: cantharidin, obtained from the beetle *Lytta vesicatoria;* phrynin, contained in the secretions from the cutaneous glands (parotid) of toads; the secretions from the poisonous glands of snakes and scorpions; the secretions from the sting-glands of bees, wasps, and hornets; the secretions from the salivary glands of stinging gnats, flies, and horse-flies; the secretions from the poisonous glands of the maxillary proboscis of spiders (Tarantula), which produce local necrosis or give rise to inflammation. Finally, many of the *higher plants* produce substances which, when brought in contact with the tissues, cause local irritation and inflammation. Examples are: daphne, various forms of Ranunculus, anemone, marsh-marigold, calla, dragon-root, *Croton tiglii* (producing in its seed croton-oil), buckthorn (*Rhamnus cathartica*), water-elder (*Rhamnus frangula*). These plants produce the poisonous substances either in their blossoms, or in their seeds, stems, or roots.

The character of the local changes which the substances mentioned above produce is naturally very varied, and is dependent in part upon the activity of the poison, and in part upon the place and manner of its application. Mineral salts, liquor potassæ, and strongly concentrated corrosive-sublimate solutions produce marked eschar-formations, associated with severe hæmorrhagic inflammations, especially when taken into the stomach. Through the action of acids a strong demand is made upon the alkaline fluids of the body, and we find, in consequence, alterations in the respiration and the circulation. The poisons from the poisonous glands of snakes, which belong to the toxalbumins, cause usually very severe local inflammations and hæmorrhages, which often become wide-spread and sometimes occasion marked gangrene of the tissues. There are other snake-poisons which produce only slight local changes, while the systemic poisonous symptoms are by far the most marked. There is a *volatile or gaseous class of poisons* which cause local irritation of the tissues, especially of the mucous membranes of the eye and of the respiratory tract (*irrespirable gases*). To this class belong the fumes of ammonia, chlorine, sulphuric acid, nitrogen monoxide, nitrogen dioxide, nitrogen trioxide, osmic acid, and mustard-oil. The intensity of action of these poisons varies also, often occasioning mere temporary redness, but being able also to produce severe inflammation and necroses of tissue. From the irritation of the respiratory tract coughing is produced, and by spasm of the larynx the breathing may be interfered with.

There are added, in many cases, to the local irritation and inflammation caused by the action of this class of poisons, further *effects upon the internal organs.* After the absorption of these poisons by the juices of the body, those organs suffer most, as a rule, in which the poison is retained or elaborated, although the action may extend also to those organs which do not take part in the excretion of the poison. After the application of certain poisons the lesions at the point of entrance are transient and unrecognizable. The first recognizable anatomical lesions occur in tissues to which the poison has been carried by the blood. Finally, a given poison may act as a *nerve- and heart-poison*, so that, clinically, this action appears more prominently than the local tissue-degeneration. After corrosive-sublimate poisoning, cell-necrosis takes place in the secreting portion of the kidneys, combined with marked inflammation of the colon. Salts of chromic acid, cantharidin, and many acids cause more or less marked tissue-necrosis and inflammation in the secreting portion of the kidneys and in other parts of the urinary tract.

Phosphorus, arsenic, and antimony, which are but mildly corrosive, produce tissue-degenerations, principally of a hæmorrhagic or fatty nature, in the kidneys, liver, heart, muscles, and capillaries of different organs. These changes are seen especially after phosphorus-poisoning.

If an individual is exposed for months or years to the vapor of yellow phosphorus, it may produce an inflammatory necrosis of the jaw-bones; but this necrosis only takes place when the inhalation of the vapor is combined with such conditions as putrid decomposition in the mouth, or decayed teeth. In growing bone small doses of phosphorus, frequently repeated, can produce an increased osteogenesis.

After the long-continued use of nitrate of silver, black silver-deposits may be found in the most diverse tissues of the body—in the skin, in the kidneys, in the intestinal villi, and in the choroid plexus of the brain.

The snake-poisons possess, in addition to their local irritant action, a paralyzing effect upon the nervous system and the heart. So after snake-bite we may have death from paralysis of the centre of respiration.

Solutions of lead, when taken into the alimentary tract, may have a corrosive action on the mucous membrane, giving rise to inflammation, and producing such intestinal symptoms as vomiting, diarrhœa, constipation, and gastric cramp, associated with such nervous symptoms as anæsthesias, motor palsies, convulsions, faintings, and unconsciousness. If lead be ingested continuously for a long time, general disturbances show themselves, such as derangements of digestion, intestinal colic, pain in the limbs, anæsthesia, motor palsies, disturbances of cerebral activity, and kidney-disease. These various lesions are undoubtedly dependent upon the dispersion and deposition of lead in the body, leading to the most wide-spread anatomical changes.

The active poisonous principles of *ergot* (*Secale cornutum*) are *sphacelinic acid* and *cornutine*. When taken in large doses, as continuously in bread, this drug causes itching, pains, cramps in the extremities, and, later on, numbness and a feeling of cold in the tips of the toes and fingers. This condition may go on to more or less wide-spread gangrene and sloughing of the parts, with the formation of ulcers in the intestines (*ergotism*, *itching disease*). These results are attributed by von Recklinghausen and Kobert to peculiar changes in the arteries due to the action of the ergot. In long-continued poisonings, degenerations take place in the spinal cord (Tuczek).

§ 10. *Poisons which cause changes especially in the blood*, and hence may be called **blood-poisons,** are partly gases and partly fixed substances which are absorbed. The latter are absorbed principally from the intestinal tract: they may, however, enter the body through wounds, or they may be injected directly into the blood-vessels. Sometimes these blood-poisons produce also a local action upon the tissues at the point of entrance; again, there may be joined to the action on the blood a direct influence upon the nervous system, producing death under certain circumstances, even before the action upon the blood has been recognized. Finally, it should be noted that the blood-changes induced by the poison may produce secondary diseases in the different organs, as, for instance, the kidneys, the liver, the intestines, and the brain.

The most important blood-poison is undoubtedly *carbon-monoxide gas*, which causes an effect upon the blood, and very frequently produces more or less serious or deadly poisonings. Most frequently the poisoning occurs from the carbon monoxide contained in coal- or illuminating-gas. This gas may also be produced after the burning of gunpowder or gun-cotton.

The action of the carbon monoxide taken in by breathing consists largely in its combination with the hæmoglobin, forming carbo-oxy-hæmoglobin. This combination decreases the amount of oxygen in the hæmoglobin and hinders the taking up of oxygen by this substance, even when the respired air contains as low as 0.05 per cent. or 0.02 per cent. of CO (Gruber). The blood-corpuscles are not changed in appearance by this poison. If a sudden addition of carbon monoxide reaches the nervous system, it may produce direct injury to it, giving rise to cramps and, later on, to paralysis (Geppert, Kobert). In cases of poisoning lasting for a long time, the displacement of the oxygen in a large portion of the blood-corpuscles may produce tissue-asphyxia. If the poisoned individual does not die, he may suffer from disturbances of the nutrition of various organs of the body, especially of the nervous system. The poisoning itself is characterized by headache, tinnitus aurium, fainting, malaise, vomiting, giddiness, cramps, palsies, and coma. The blood itself turns a pale-violet or cherry-red color on account of the increase in carbon monoxide, and the internal organs have a peculiar bright-red color.

A second not infrequent form of poisoning is that produced by *hydrocyanic acid* (CNH), which, in combination as *potassium cyanide* (CNK), is much used in the arts. In general, hydrocyanic acid is found in unstable combination in the leaves, barks, and seeds of very many plants: bitter almonds, cherry- and peach-stones, apple-seeds, leaves from the common laurel, the rind of *Prunus padus*, the root-bulbs of many of the Euphorbia, flaxseed, etc.

Hydrocyanic acid possesses a double action. In relatively small doses it exerts a paralytic influence upon the central nervous system, and death may be produced in a short time—even in a few seconds—by paralysis of the centres of respiration or of circulation. Besides this, there is an action upon the blood and tissues, robbing them of their ability to unite with and use oxygen (Geppert), so that these organs suffocate in the presence of oxygen. According to Kobert, there is formed a cyan-methæmoglobin which appears bright red in color and produces a bright-red appearance of the cadaveric lividity.

Among the third class of poisonous substances which should be named in this connection is *hydrogen sulphide* (H^2S), which is formed in the vapors of sewers and dung-pits, and which may produce sudden death by paralysis of the nervous system, when inspired in large amounts. By long contact with blood containing oxygen, as may usually be seen in decomposed corpses, sulphur-methæmoglobin is formed, the blood becoming greenish in color.

Apart from their direct action on the nervous system, carbon monoxide, hydrocyanic acid, and hydrogen sulphide produce deleterious effects by lowering the functional powers* of the red blood-cells, through combination with the hæmoglobin.

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* The words in the original text are—"die functionellen Lähmungen"; but the latter is doubtless a misprint for "Leistungen."—TRANSLATOR'S NOTE.

Another large group of poisons injure the blood chiefly by destroying the red blood-corpuscles and forming methæmoglobin. By methæmoglobin we understand a combination of oxygen with the hæmoglobin; the amount of oxygen present in the combination being the same as in oxyhæmoglobin. The hæmoglobin, however, has been bound up with the oxygen into a more stable chemical compound than oxyhæmoglobin. Such an action is produced by oxidizing substances, as ozone, iodine, sodium hypochlorite, chlorates, nitrites, and nitrates; by reducing agents, as nascent hydrogen, palladium hydride, pyrogallol, pyrocatechin, hydrochinon, and alloxantin; and, finally, by substances which act differently from either of these, as aniline salts, toluidin, and acetanilide. In the change from hæmoglobin to methæmoglobin through oxidizing agents, oxyhæmoglobin is present as an intervening stage.

The production of methæmoglobin can take place as well in the blood-corpuscles as in the coloring-matter which has escaped into the blood-plasma; but the destruction of blood-corpuscles and the escape of hæmoglobin into the blood-plasma are not always followed by the formation of methæmoglobin. In case of such a marked destruction of red blood-cells as occurs in poisoning from phallin, helvellic acid, and arseniuretted hydrate, only a portion of the hæmoglobin is changed into methæmoglobin. Hæmoglobin and oxyhæmoglobin have a red color, methæmoglobin a sepia-brown color.

Dissolution of the red corpuscles and the formation of methæmoglobin is seen after poisonings which have produced marked local tissue-changes, as, for instance, poisonings with acids, salts of the metals, and phosphorus; but a great number of other substances have the property of attacking the blood and changing the coloring-matter.

Phallin, a toxalbumin which is found in mushrooms (*Amanita s. Agaricus phalloides*), the *helvellic acid*, which occurs in fresh *Helvella esculenta* and is lost if the fungus be dried, and *arseniuretted hydrogen* ($AS.H^3$) have a very dissolving action on the red blood-corpuscles, and, in consequence, produce an increased formation of biliary pigment, as well as a deposition of the derivatives of the blood-coloring matter in the liver and kidneys.

Potassium chlorate (CLO^3K), *pyrogallol* ($C^6H^6[OH]^3$), *hydrazine* ($H^2N{-}{-}NH^2$), *toluylendiamine* ($C^6H^5[NH^2]^2CH^3$), *nitrobenzol* ($C^6H^5NO^5$), *nitroglycerin* ($C^3H^5[ONO^2]^3$), *amyl nitrite* ($C^5H^{11}NO^2$), *picric acid* ($C^6H^2[NO^2]^3OH$), *aniline* ($C^6H^5NH^2$), *carbon disulphide* (CS^2), are distinctive in their action, in that they sometimes cause the destruction of the red blood-corpuscles in the formation of methæmoglobin, and they sometimes do not.

After a very large dose of potassium chlorate, death may occur in a very few hours, through destruction of the blood-corpuscles and the action of the potassium, with the development of vomiting, diarrhœa, dyspnœa, cyanosis, and weakening of the heart. The blood in these cases is of a chocolate-brown color. In more protracted cases of poisoning with small doses we find the products of the destruction of the blood in the spleen, liver, marrow of the bones, and kidneys; and the urine may show a reddish-brown to black color (methæmoglobin). The presence of delirium, numbness, coma, and cramps during the illness shows that the central nervous system is markedly affected. Pyrogallol produces similar symptoms. Hydrazine and phenyl hydrazine produce multiple ecchymoses, besides the destruction of the red blood-cells, with the production of methæmoglobin. The main feature of toluylendiamine-poisoning is the breaking up of the red blood-corpuscles, which leads to the deposition of iron-containing pigment in the spleen, liver, and bone-marrow. According to Stadelmann, hæmoglobin and methæmoglobin are not found in the urine, or, at least, only in small amounts. In picric-acid poisoning there is marked disturbance of the central nervous system, which is characterized by severe cramps, in addition to the changes in the blood and the production of methæmoglobin. In a similar manner, aniline and carbon disulphide not only cause changes in the blood, but also act harmfully by paralyzing the nervous system.

In the *last group of blood-poisons*, as the chief representatives, are to be named *ricine*, derived from the seed of the castor-bean, and *abrin*, found in the seed of the *Abrus precatorius*, which belongs to the Papilionaceæ. The entrance of these poisons into the blood *produces a coagulation* similar to that produced by the fibrin ferment. *Ricine* is very virulent, and may be absorbed from wounds and from the alimentary tract, producing weakness, vomiting, colic, bloody dejecta, icterus, cramps, and anuria. In the intestine, at spots where the ricine has formed thrombi in the vessels, ulcers may be found.

Abrin is also very poisonous, and, when introduced into the blood in doses of a few hundredths of a milligram per kilo of the body-weight of the animal, can produce death (Kobert). Upon the mucous membrane it produces, even when very dilute, coagulation in the blood-vessels, and, later on, inflammation.

§ 11. The last group of poisons, which are generally classed together as **nerve- and heart-poisons**, are principally characterized by the fact that notwithstanding the severity of the symptoms, which show themselves in the form of irritations and palsies, anatomical changes are either not susceptible of being recognized, or at least they are not so in a manner that can be looked upon as characteristic in a given case of poisoning. This is especially the case when the poison produces death very quickly; for during the course of protracted poisoning, or chronic poisoning from small doses extending over months and years, anatomical changes very easily recognized are often found—a fact which shows that these poisons do not solely produce functional changes in the nervous system, but more frequently produce a damaging effect on the cell-protoplasm, which finds expression in degenerations.

Among the very numerous *poisons which act especially upon the nervous system*, and thus may produce death through its paralysis, belong, as the most important members: chloroform, ether, hyponitrous oxide, alcohol, chloral hydrate, opium and its alkaloid morphine, cocaine, atropin, hyoscyamine, daturine (*Stramonium atropin*), nicotine, coniine, cicutoxin, santonin, camphor, quinine, veratrine, colchicine, aconitin, strychnine, cytisin, and curarine.

As *heart-poisons* are to be especially noted: digitalin, helleborin, and muscarine.

Chloroform ($CHCl^3$) acts in an irritating manner when applied directly to the mucous membranes, and may produce transitory inflammations. When it is inhaled, or when it is conveyed to the blood by means of the intestinal tract, there ensues, after a short period of excitation, a diminution of the irritability of the gray and the white matter of the brain. According to Binz, a slight coagulation of the protoplasm of the ganglion-cells is produced. Death may be caused by paralysis of the central nervous system, as well as through early stoppage of the heart

—the latter, however, occurring only when the heart is abnormally weak or degenerated, though perhaps also when the irritation produced by the chloroform upon the mucous membrane of the nose causes an unduly strong excitement of the inhibitory nerves of the heart. Finally, long-protracted exhibition of chloroform may produce degenerative changes in various organs, as the heart, kidneys, liver, the muscles, and the blood.

Ether (diethyl ether, $C^2H^5.O.C^2H^5$) acts similarly to chloroform, yet it is less poisonous and acts less detrimentally upon the functional activity of the heart.

Hyponitrous oxide (N^2O) acts especially upon the cerebrum, destroys sensation of pain, and paralyzes consciousness; later on, the action extends to the spinal cord, the medulla oblongata, and the heart.

Alcohol (C^2H^5OH), after temporarily producing excitement, acts as a depressant and paralyzant of the brain, and produces at the same time a dilatation of the arteries of the skin, so that in a drunken person a severe chilling through the skin can easily take place. Death can follow suddenly, in a manner similar to what is observed in apoplexy; more frequently it produces a gradually deepening loss of consciousness and sensorial perception, the breathing becomes slower, the pulse small, the countenance cyanotic; complete coma and general paralysis close the picture. The immoderate use of alcohol extending over months or years may produce, on the one hand, pathological accumulations of fat in the regions where fat is normally to be found, and, on the other hand, it may cause degeneration of the glandular organs, especially the kidneys and liver, followed by overgrowth of the connective tissue, with atrophy of the liver and kidneys, and, in addition, sclerosis and atheroma of the arteries, degenerations in the brain, etc. It is, however, impossible to say at the present time in what manner, how frequently, and to what extent these symptoms belong to the use of alcohol. It is certain that the drunkard frequently suffers from indigestion, diseases of the circulation, laryngitis, pharyngitis, bronchitis, and disturbances of the cerebral functions, and that the disease of the brain which is produced by alcoholism and is called delirium tremens is marked by twitchings of the muscles, obstinate sleeplessness, anxiety, and hallucinations.

Chloral hydrate ($CCl^3.CHO.H^2O$) has a local irritating action on the mucous membranes, and a paralyzant action through the blood upon the brain, spinal cord, and heart, and thus produces sleep. When death occurs from an overdose, deep coma and relaxation of all tissues are observed, with œdema of the lungs.

Opium and *morphine* ($C^{17}H^{19}NO^3$) produce depression of the functions of the brain, leading to sleep, though in some persons this is preceded by a condition of excitation. Large doses produce unconsciousness, muscular paralysis, slowing and weakening of the action of the heart, contraction of the pupils, slowing of intestinal peristalsis, diminution in the exchange of gases in the blood, and an inhibition of the normal irritability of the respiratory centres. There are no characteristic post-mortem lesions; the blood is dark and liquid. Chronic opium-ingestion may produce disturbances in digestion, dizziness, sleeplessness, neuralgias, imbecility, impotence, anæmia, hallucinations, tremors in the hands, fever, etc., which may vary much in different individuals. The system in chronic morphinism becomes accustomed to increasingly larger doses; withdrawal of the drug produces severe nervous symptoms, and, under certain conditions, dangerous collapse.

Cocaine ($C^{17}H^{21}NO^{4}$) produces peripheral dulling of the sensibility of the terminal sensory nerve-filaments; centrally, first irritation, then paralysis. The chronic cocaine habit may produce symptoms similar to those seen in chronic morphinism.

Atropin and *hyoscyamine* ($C^{17}H^{23}NO^{3}$), alkaloids which are found in the members of the order Solanaceæ (deadly nightshade, thorn-apple, and hyoscyamus), have a paralytic action on the peripheral nerve-filaments, and finally irritate and then paralyze the centres. A solution of atropin introduced into the eye produces dilatation of the pupil and paralysis of accommodation for near vision, through its action on the terminal fibres of the oculo-motor nerve in the iris. Atropin may further inhibit the secretion of glands (as the submaxillary); under its action, also, intestinal peristalsis ceases through deprivation of the necessary nerve-stimulus. Through the action of this poison on the brain we may have excitation, gaiety, laughter, leading even to insanity and madness, followed by paralysis. Post-mortem examination is negative.

Nicotine ($C^{10}H^{14}N^{2}$), a volatile alkaloid found in the tobacco-plant, acts upon both the peripheral and the central nervous system, producing nausea, salivation, vomiting, diarrhœa, dizziness, muscular weakness, headache, convulsions, delirium, and paralysis. Chronic nicotine-poisoning may be followed by nervous diseases and disturbances of the heart's action. According to Vas, there is both in chronic-alcohol and nicotine poisoning a characteristic degeneration of the ganglion-cells, the chromatin structure becoming homogeneous.

Coniine ($C^{8}H^{17}N$), an alkaloid of hemlock, acts as a paralyzant of the peripheral motor terminal nerve-fibres, irritating and then paralyzing the central nervous system. *Cicutoxin*, a poisonous resin extracted from the water-hemlock (*Cicuta virosa*), causes nausea, vomiting, attacks of colic, palpitation of the heart, cramps, and unconsciousness.

Santonin ($C^{18}H^{18}O^{3}$) produces cramps originating in the brain and spinal cord, with benumbing of the sensorium, vertigo, vomiting, salivation, and yellow vision, or xanthopsia, in which white is seen as yellow and blue as green.

Quinine ($C^{20}H^{24}N^{2}O^{2}$), the most important of the numerous vegetable alkaloids, found in the bark of cinchona and other plants of the same order, acts in a paralyzing manner upon the living protoplasm, and in relatively small doses inhibits the functional capacity for work of the cerebrum. Large doses produce death by paralysis of the centres of respiration and of the heart.

Aconitin, *colchicine*, and *veratrine* produce local irritations and, later, benumbing of the peripheral endings of the sensory nerves. On the central nervous system they act as irritants and finally as paralyzants.

Strychnine ($C^{21}H^{22}N^{2}O^{2}$), derived especially from the plant nux vomica, causes increased reflex irritability of the nerve-centres, so that the slightest external irritation produces tetanic convulsions. Death may occur in from ten to thirty minutes after the first attack of convulsions, and results through central paralysis—namely, of the vaso-motor centre.

Curarine ($C^{19}H^{35}N$), the most active principle of the arrow-poison curari, which is probably derived from the cortical portion of the roots of many plants of the Strychnia family, paralyzes in small doses the terminal fibres of the musculo-motor nerves. Larger doses paralyze the central nervous system and the vaso-motor nerves, after a temporary excitation.

Digitalin and *digitalein*, two glucosides obtained from the foxglove, act locally as irritants, and also exercise, after absorption, an irritating action on the heart, vagus-centre, and muscular fibres of the blood-vessels, so that there is produced, by the slowing of the heart, an increase in blood-pressure. Larger doses produce headache, delirium, ringing in the ears, irregularity in the frequency of the heart's action, convulsions, and coma.

Helleborin, a glucoside from hellebore, acts similarly to the preparations of digitalis.

Muscarine ($C^5H^{15}NO^3$), the poison of the fly-mushroom, acts as an irritant upon those peripheral nerve-filaments which atropin paralyzes. In poisoning by muscarine, death takes place not from paralysis of the heart, but from the intense excitation of the inhibitory centres producing stoppage of its action. In general, after the ingestion of this poison, we have salivation, vertigo, anxiety, nausea, vomiting, diarrhœa, convulsions, and finally unconsciousness. Small doses produce a condition similar to that seen in inebriation, with a state of excitation.

In the foregoing summary of poisons, which necessarily comprises but a superficial examination of a few out of the entire number of such agents, I have in general followed the arrangement in groups used by Kobert in his "Textbook on Intoxications." A deeper knowledge than that which we have at present concerning the physiological action of these poisons will probably lead in the future to another mode of classification. Loew* has lately attempted to make a classification of poisons according to their action on the manifestations of life—i.e., upon the living protoplasm. He divides them into two large groups—namely, *general poisons*, those which, in moderate concentration, act fatally upon the entire organism; and *special poisons*, those which do not injure certain classes of organisms. The *general poisons* are characterized chiefly by their power to change the chemical character of the proteids out of which the living protoplasm is formed. Among these can be differentiated: 1, *oxidizing poisons* (ozone, chromic acid, manganic acid, hypermanganic acid, hypochlorites, hydrogen peroxide, chlorine, bromine, iodine, phosphorus, and arsenious acid); 2, *poisons having a catalytic action* (ethyl ether, chloroform, chloral, many carbohydrates, etc.), which transfer to the protoplasm the unstable condition of their molecules, and thus tend to produce chemical changes in the unstable (*labilen*) albumin; 3, *poisons acting by the production of salts* (acids, soluble mineral bases and caustic alkalis, alkaline earths, and salts of the heavy metals), which form chemical combinations in the proteid materials; 4, *substitution-poisons* (hydroxylamine, diamide, phenyl hydrazine, ammonia, carbolic acid, hydrocyanic acid, etc.), which even when greatly diluted interfere with the aldehyde- or amido-groups. *Special poisons* are classified as: 1, *toxic proteids*—i.e., (*a*) *toxalbumins* (produced by bacteria and poisonous to animals), (*b*) *alexins* and *immunitoxins* (produced in animals physiologically or pathologically, and poisonous for bacteria), (c) *vegetable enzyms* (abrin and ricine, produced from phanerogams and the higher fungi, and poisonous to animals), (*d*) *animal enzyms* (produced by certain animals, snakes, fishes, and spiders, and poisonous to other animals); 2, *organic bases* (strychnine, atropin, curari, etc.) having an unknown action; 3, *poisons working indirectly*, which interfere with the processes of respiration (carbon monoxide, sulphites), or act as poisons through decomposition (nitrites, iodine combinations), or act destructively through changes in the formative conditions of organized tissues (neutral salts of the alkalis, the alkaline earths, oxalates).

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* "Natürliches System der Gifte," München, 1893.

3. *Origin of Diseases through Infection or Parasitism.—Miasms and Contagions.—Vegetable and Animal Parasites.*

§ 12. As we have seen in §§ 8–11, there occur, in the intoxications, morbid vital phenomena which are produced by definite chemical substances, the mode and severity of their action being dependent upon the character of the poison and the dose employed—that is, if the idiosyncrasies of the subjects of the poisoning and the special mode of application of the poison are not taken into consideration.

In those **diseases which arise from infection,** and therefore are called **infectious diseases,** we have, on the contrary, to deal with *diseased vital phenomena* which, if we disregard the individual susceptibility of the infected person and the peculiar mode of entrance, into the body, of the infecting material, are dependent solely upon the character of the infecting agent; while the amount of the dose, if it possesses any significance, has at least only a subordinate one.

The explanation of this difference between intoxication and infection consists in the fact that, in the first case, intoxication, the poison does not increase within the body, while *in infection the harmful substance increases after its entrance into the organism,* so that amounts of infective material so small as to be utterly inappreciable by us suffice to produce the severest fatal diseases. The dose, or quantity, of infecting material has this influence, therefore, upon the succeeding illness—namely, that a larger amount makes the infection more probable; that is, the reproduction of the injurious material within the body takes place more rapidly, and the constantly increasing material of infection will therefore in a shorter time attain such proportions that pathological processes must develop in the tissues, and must at the same time be accompanied by recognizable symptoms.

The injurious elements which are produced by infectious diseases always find their way from the outer world into the human organism, and cause *an illness which may follow a pathognomonic course;* and from the peculiarities of this course it is possible to conclude that we are dealing with a specific variety of injurious influence—one that behaves in an entirely characteristic manner. In pregnant women the infectious matter may be transmitted from the organism of the mother to her child *in utero.*

If an infectious disease attacks a number of individuals in a given locality, it is termed either a **pestilence** or an **epidemic.**

A study of professional observations shows that, in a certain number of cases, the noxious influence producing a certain infectious disease manifests its activity in certain localities, causing sickness among the people of a given district. In other cases contact with the diseased person, or proximity only, or using something which that person has used, or still other ways—as, for instance, through dejecta or sputum upon uncleaned objects—may produce the disease. Finally, it may occur that infecting material is produced only occasionally in a given locality, and only when a patient visits that particular region and by his presence leads to the production there of the infectious material. Out of the various conditions enumerated, occasion has been taken to divide the matters which are capable of producing infectious diseases into various groups and to designate these under particular names. If infectious material is connected with a certain locality it is called a **miasm**, and receives this name on the ground that the particular region produces the infectious material. If one particular region alone produces the disease it is termed a *local miasm*, and if present everywhere it is termed a *ubiquitous miasm*. To these miasmic diseases belong especially malaria, and also croupous pneumonia, articular rheumatism, many wound-inflammations, septic osteomyelitis, and ulcerative endocarditis.

When the infection is carried directly from man to man, and spreads through houses, villages, cities, and countries, it is termed a **contagium**, and it is consequently understood that the place in which the organism grows is within the human body, or it may be also in some inferior animal, while outside of the human or animal body neither production nor multiplication of the infecting material takes place. To such contagious diseases belong smallpox, measles, scarlet fever, diphtheria, erysipelas, pyæmia, phlegmon, typhus fever, relapsing fever, anthrax, hydrophobia, gonorrhœa, whooping-cough, influenza, many catarrhs of the mucous membranes, tuberculosis, syphilis, glanders, and leprosy.

When an infectious material is characterized by the fact that it develops in a certain district only when a patient suffering from the disease chances to visit this particular locality and there gives rise to an outbreak of an epidemic, we have what is called a **miasmatic-contagious disease**; the assumption being warranted, under these circumstances, that the infecting matter had spread from the organism of the first patient, had then multiplied at some given spot, and finally had of itself, or with the help of certain local influences, attacked the resident population of the locality in an epidemic fashion. Such miasmatic-contagious diseases are cholera, typhoid fever, dysenteries, yellow fever, and the plague.

The nature of the causes of these miasms and contagious diseases remained concealed from the older practitioners. If such an infectious disease made its appearance in the form of a plague or epidemic its cause was sought in cosmic and telluric conditions, and it was spoken of as a *constitutio epidemica* or a *constitutio pestilens*. Only within the last few decades has our knowledge of the etiology and nature of infectious diseases made true progress, and it has been shown that infectious diseases are **parasitic diseases** *whose origin is attributable to an increase of small living organisms within the human body*. While it is true that only some of the infectious diseases are known positively to be produced by parasites, it is most highly probable that all are due to such agency. The proofs that the causation of infectious diseases is thus related to living substances capable of reproduction—to a *contagium animatum*—are deduced principally from: first, the fact that the deleterious influence produced by a certain infectious disease, where it is once present, continues to renew itself endlessly, so that from a single case innumerable others may be infected; secondly, the fact that a minute and imponderable amount of infectious matter is sufficient to convey disease to an individual, and afterward to produce effects of the most striking character upon the organism of this individual—circumstances which could scarcely be explained in any other way than by assuming that the detrimental substance actually multiplies itself within the human body.

The attempt has been frequently made to explain the manifestations of infection through the action of noxious gases or soluble ferments. These hypotheses, however, are wholly insufficient; for they either leave the phenomena which are observed in the course and spread of these epidemics unexplained, or else the explanations adduced are open to well-founded objections.

The parasites which are capable of causing infectious diseases belong to the lowest orders of the vegetable and animal kingdoms. Among the plants the **Schizomycetes** or **bacteria** are the most important; among the animal parasites the smallest of living protoplasmic bodies, called **Protozoa**, play a prominent part. Among the more highly organized plants are the **Saccharomycetes** and **Hyphomycetes**, whose pathogenic importance is much less than that of the bacteria. Among the animal **parasites** occurring in man are a number of **worms** (Nematoda, Trematoda, and Cestoda) and **Arthropoda** (Arachnida and insects). Their action is, however, markedly limited, and the pathological conditions produced by them are not generally classified as infectious diseases in the true sense of that term.

For the production of a true infection a given parasite must increase and reproduce itself through a number of generations within the human body, and must spread more or less widely throughout the tissues. This definition being accepted, and at the same time the itch-insect being excluded (for it reproduces many generations in the skin), we must place in this class only the parasitic Schizomycetes, Saccharomycetes, and Protozoa. The majority of the more highly organized animal parasites live only a portion of their lives within an individual organism—i.e., within the same host. Such parasites as multiply within the invaded organs by means of the production of eggs or of formed offspring are devoid of the power to become again reproductive in the same host.

Parasitic infection—i.e., the entrance into the human body, and the increase, of a parasite—can occur in almost every portion of the body. The most usual seats of infection are the mucous membranes that are most easily accessible from without, particularly the intestinal and respiratory tracts. In many cases the parasites are introduced in the food and the drink, especially in water. The pathogenic organisms being for the greater part very small and easily suspended in the atmosphere, they are by this means carried about everywhere. They are often obtained from respired air, and are found distributed partly in the respiratory tract, partly in the alveoli of the lungs, where they remain clinging to the walls, and frequently are taken up into the tissues.

Wounds form a broad field for the entrance of small parasites. Becoming infected by means of the air, or from contact with unclean fluids or with solid objects, they thus furnish the starting-point of an infection. Finally, many parasites can attack an injured cutaneous surface, and there increase, giving rise in this manner to infectious diseases.

The belief that certain diseases, as the plague, were of parasitic origin, is very old, and found expression in the works of Kircher (1602–1680), Lancisi (1654–1720), Linné (1707–1778), and others. Confirmation of the parasitic origin of infectious diseases, however, has been obtained only in these later times. A few decades ago Henle, Liebermeister, and others put forward the belief that only upon the assumption of a *contagium animatum* could we explain the peculiarities of infectious diseases; but it is only within the last twenty years that the doctrine of their parasitic origin has obtained a really firm foundation.

The influence which **climate** exerts upon man—the effects of temperature being left out of the account—is essentially dependent upon the consideration whether or not the special micro-organisms which have the power of producing disease develop in the soil of that particular locality. A harsh, rough, windy climate may thus be healthy, while one that is mild and subject to but slight variations of temperature may be an unhealthy one. In well-populated regions the question naturally arises whether infectious diseases are to be found among the inhabitants. Periodic fluctuation in the virulence of the noxious influence in a certain climate is partly dependent upon the fact that micro-organisms do not multiply in the same ratio at all seasons, and partly upon the fact that pathogenic micro-organisms present in the soil do not always get into the drinking-water and into the atmosphere, or at least are only occasionally brought in this manner into the human organism.

According to Pettenkofer, the spread of miasmatic-contagious diseases—as, for instance, cholera—is not to be explained by the fact that the bacteria from the dejecta of a patient are able to survive outside the body for a given length of time, and under favorable circumstances to develop, and then through drinking-water, food, or unclean hands to find their way into the mouth and the intestinal tract, and again cause cholera in the human subject. He believes, rather, that the infecting germ, having reached the soil, is capable of producing its characteristic poison only when certain temporary local conditions are present—that the poison there increases its virulence by reason of its combining with an unknown something due to certain conditions of the soil, in order to be capable of reproducing the poison of the disease. The latest researches concerning the etiology and spread of typhoid fever and cholera have not confirmed this supposition; they point, instead, to the fact that the bacteria of cholera and typhoid fever are sufficient in and of themselves, in certain cases, to produce infection. It follows from what has already been said that cholera-bacteria, when introduced into the alimentary tract of man, or into that of certain animals, may produce the disease known as cholera.

§ 13. The **disease-producing bacteria** are very small, unicellular masses of protoplasm, which appear in the form of little spheres (cocci) and fine, straight, or curved rods (bacilli and spirilla), frequently uniting among themselves to form peculiar combinations. Some of them multiply in the outer world, and thence occasionally enter the human body. Others, on the contrary, are so constituted that they cannot multiply in the outer world, and only reproduce themselves when within the human or animal body. *Bacteria have therefore been classified as ectogenic and endogenic;* the first are identified with the *miasmatic diseases*, the second with the *contagious*. This division cannot, however, be strictly adhered to, since some bacteria that generally multiply only within the animal organism may, under certain conditions, develop outside these organisms; so that, in a certain sense, a contagium may become a miasm.

On the other hand, it is not necessary for the spreading of a disease caused by ectogenic bacteria that the Schizomycetes shall multiply outside the human body; there occurs more frequently an infection from individual to individual. For instance, the bacillus of anthrax can multiply in the outer world as well as in animal tissues, and the spread of the disease may occur through direct infection of one person by another, or of a human being by an animal, equally as well as by the man or animal receiving the infection from culture-media of any kind. The cocci which produce suppuration, or those of inflammation of the lungs, can infect a hitherto healthy individual directly from the outer world where they have been propagated, quite as well as from another diseased individual.

Therefore it is impossible to draw a definite boundary-line between miasms and contagions, or between ectogenic and endogenic bacteria. This distinction has, indeed, as yet no great value, except that in many infectious diseases one of these two forms predominates, and there are infections concerning which we know of but one mode of spreading. Thus, for instance, smallpox and measles, whose infecting materials have not yet been discovered, are diseases in which spreading is only known to occur through direct and indirect contagion; and similarly, we are warranted in assuming that the poison of syphilis cannot multiply outside the human body.

Outside the human body pathogenic bacteria are found both in solids and in liquids, and also in the air. In regard to those forms which may increase outside the human body (the bacteria of cholera, of typhoid fever, of anthrax, of suppuration, and of actinomycosis), they are found to be contained in the water fouled by organic substances, in moist soils rich in organic substances, and in dead animal or vegetable tissues containing moisture. They are, besides, often present in dry earths and dried tissues, and from these can pass into the air, as well as from fluids. Thus severe wind-storms, clouds of dust, and sprinkling the streets favor their distribution. It is true that, in the drying of substances containing bacteria, some die, since they cannot survive complete desiccation. Many of the pathogenic bacteria, however, produce *a resistant form* (*spores*), and are thus able to resist thorough drying, and consequently to maintain their vitality in the air. If in this condition they come in contact with solids or fluids, and become attached to them, they may remain alive here for a long period; and if the circumstances are favorable—i.e., if they find a proper nourishing material and the necessary water, and if the temperature of the locality reaches the height necessary for their development—they may again multiply.

If bacteria which cannot, under normal conditions, propagate their kind outside the living animal tissues, exist for a long time outside the body, it is because they produce forms which withstand drying (tuberculous bacilli) or which are not immediately destroyed by chemical products in the surrounding fluids, moist earth, or the tissues in which they lie. For a limited time these organisms can cling to the most varied objects and yet live, producing for a while the danger that individuals may become infected from objects not properly cleaned. If the bacteria live in spite of drying, the dust of the streets, of the floors and walls of houses, as well as the air itself, may contain bacteria, especially when they are thrown off in large numbers. This is especially true of the *Bacillus tuberculosis*, since in pulmonary tuberculosis the sputum, in intestinal tuberculosis the fæces, and in urogenital tuberculosis the urine, contain a great number of these organisms.

According to Koch and others, the superficial strata of the earth contain many cocci and bacilli, some of which are pathogenic. If the soil is very dry it contains only those bacilli which produce forms that withstand drying (spores). With increasing depth there is a proportionate decrease in the number of bacteria, until at one metre below the surface there are practically none. Water coming from very deep springs or wells contains very few bacteria, or is sterile. Bacteria which may be present in still water increase in numbers very rapidly, and if the water contains sufficient nutrient material pathogenic bacteria (typhoid-fever and cholera bacilli) may be found. Other forms of pathogenic bacteria may remain virulent and capable of propagation in water only for a short time.

Sea air at some distance from the coast contains very few micro-organisms.

§ 14. **Bacteria** usually **enter the system** through the mucous membrane of the intestinal or the respiratory tract, or through external wounds. Not infrequently they enter the sound skin, by means of the openings of the hair-follicles or of the sebaceous glands. Under special conditions (coitus, operative measures, dribbling of urine) the infection may take its start from the mucous membrane of the genito-urinary tract. Certain cases of infection may be due to insects which have taken up bacteria with the diseased blood or secretions of men or animals. These insects may have become outwardly infected by the micro-organisms, and then may have deposited the latter on some denuded or ulcerated area of the human skin or mucous membrane, by means of their oral apparatus for piercing the skin and sucking the blood, or by scraping them off their legs upon such exposed spots. If the flesh of an animal containing bacteria be eaten, and if the animal while alive were suffering from an infectious disease which also occurs in man, this particular disease may be transmitted to man, unless the bacteria have been previously destroyed.

The bacteria arrive at the point of entrance sometimes in company with chemically active substances, as in the intestinal tract, and sometimes without these substances, as in the respiratory passages and lungs; and yet at times chemical poisons may also find their way into the lungs along with bacteria, and so, too, may bacteria find access to the intestinal canal without the effective aid of any other material.

The **injurious chemical substances which accompany the bacteria** may occur as *accidental admixtures of the food*, or of the water used either for drinking purposes or for the cleansing of wounds; or they may be contained in the respired air; but they are more frequently the **products of the bacteria themselves.** All bacteria, including the non-pathogenic, produce (see Section IX.), within the tissues from which they derive the nourishment necessary for their growth, certain changes which are called fermentation and putrefaction processes, and which are very closely related to their life-activity and their powers of reproduction. Among these products of chemical metamorphosis are many which are injurious to the organisms of the higher animals and of man, since they are able to produce, in a manner similar to that described in the paragraphs devoted to poisons (§§ 10, 11), local tissue-degenerations and inflammations, changes in the blood, or symptoms of general poisoning, which may result in functional disturbances of the heart and nervous and respiratory systems. The most important of these substances are derived from albuminoid bodies, and belong to the **cadaveric alkaloids** or **ptomaines.** These substances are basic bodies, many of which are poisonous to the human body, and consequently are called **toxins.** Then we have next the **toxalbumins**—that is, *active albuminoid substances* which probably are produced and cast off by the bacteria themselves (Buchner). Neuridine, cadaverine, putrescine, neurine, and methyl guanidin are basic products derived from putrefying meat, the last three being very poisonous toxins. The bacillus of typhoid fever produces a toxin (typhotoxin) which causes palsies and increases the activity of the intestinal and salivary glands. The cholera-bacteria produce, besides penta- and tri-methyl endiamine and methyl guanidin, still other specific toxins, which irritate the intestine, render the blood incapable of coagulating, and produce muscular cramps. The tetanus-bacillus produces tetanotoxin, a toxalbumin which causes muscular spasms. According to Roux, Yersin, Brieger, and C. Fränkel, the diphtheria-bacillus, the anthrax-bacillus, the typhoid-bacillus, the cholera-spirilla, and the pus-cocci produce toxalbumins.

If these **toxic bacterial products** are introduced into the intestines or into wounds in considerable quantities with the bacteria, they may produce symptoms of **poisoning,** without a simultaneous infection—i.e., without increase of bacteria within the tissues. The same thing may also happen when poison-producing bacteria grow in the contents of the intestine, in wound-secretions, or in necrosed lung-tissues, and thus multiply as *saprophytes*. In these cases one cannot strictly speak of an infection, but must rather consider the disease which is making its appearance as an intoxication; at least it is in such cases impossible to draw a sharp line between pure intoxications and infections, since these bacteria, which originally increased in numbers as saprophytes, not infrequently also enter the tissues and multiply there.

Intestinal intoxications caused by bacterial toxins and toxalbumins occur when animal tissues or fluids decomposed by the action of bacteria are taken as food; and to these intoxications belong the greater part of the diseases termed *meat-*, *sausage-*, *fish-*, and *cheese-poisonings*. In these cases the particular poison is either introduced as such into the intestinal canal with the food, or else is formed in the intestinal tract. Decomposition and fermentation of the vegetable ingredients of diet—for instance, fermented fruit-juices, cabbage, beans, pease, etc.—exercise an injurious influence upon the intestine, or even upon the entire organism, especially if large quantities are eaten or if the offending article is used as food for a considerable period of time. In this class belongs the chronic disease known as *pellagra, Italian leprosy,* or *scurvy of the Alps,* which is met with in Italy, Spain, southwestern France, and Rumania, and is due to the eating of spoiled maize or Indian corn. This disease is characterized by gastro-intestinal affections, alterations in the skin, disturbances in the functions of the spinal cord and cerebrum, and general marasmus (Lombroso, Tuczek).

If the bacteria which have reached one of the known points of entrance are in the strict sense pathogenic, so that they give rise to an **infection,** they may multiply first in the tissues where they enter, namely, in the intestinal mucous membrane, in a wound, in the skin, etc. The *local effect* of this multiplication is dependent primarily upon the character of the bacteria (see Section IX.), and also in a measure upon the peculiarities of the tissue. In general, the local action is characterized by degeneration of the tissues, by inflammation, by necrosis, and also by regeneration; yet the condition varies very considerably in individual infections, so that in many instances the species of microbe causing the infection may be determined from the form of the local changes. It is difficult and sometimes impossible to determine in each case the exact mode of action of the multiplying bacteria; yet one may say that the processes of chemical metamorphosis called into activity by the multiplication of the Schizomycetes produce certain changes in the tissue-cells, the various chemical substances produced by the processes just referred to apparently possessing the power to kill the cells, or at least to induce degenerative changes in them, while in some instances the influence of these substances manifests itself in some form of increased cell-activity. In a certain sense, therefore, a *local poisoning* may be said to be produced by the localized-growth of the bacterial colony; and it is certain that greater importance should be attached to the effects of this local poisoning than to the mere *withdrawal of nutritive material* effected by the consumption of nourishing substances. Nevertheless the importance of such withdrawal cannot be wholly denied, for it must be recognized that the tissue-juices are often rendered unfit for the nourishment of the tissue-cells by the chemical changes effected by the bacteria, and as a result of this the cells must necessarily suffer even if no poisonous materials are produced.

The participation of the whole system in a local bacterial infection must be very slight, or may even be entirely absent, so that the disease appears as a purely local one (tuberculosis). In other cases the locally produced toxins and toxalbumins find their way into the circulating fluids of the body, and a *general intoxication* is produced—i.e., a poisonous effect is exerted upon the nervous system and at the same time upon the blood and upon the heart, and the poison thus taken into the system may produce demonstrable changes in the anatomical structure of the internal organs, especially the secreting glands, and sometimes also in the skin. In many diseases (tetanus, typhoid fever, septicæmia, and diphtheria) these poisonous symptoms are especially prominent.

If healing should not take place in the original seat of the disease, it may involve the neighboring tissues through a *continuously progressing invasion of the bacteria.* Very frequently the bacteria pass into the lymph-vessels, or into the blood-channels, and are in this manner carried off and spread over the entire body. The result of this *metastasis of the bacteria* is the *production of new colonies* at a distance from the seat of the original one, *which new colonies possess all the characteristics that belong to the primary colonies.* There are diseases (tuberculosis and suppuration) in which the number of these *metastatic colonies* is very great, so that numerous portions of the body (glands, lungs, brain, bones, etc.) may become the seats of diseased areas. In contrast to these diseases there are infections in which there is no metastasis of the bacteria from the original seat to other organs (tetanus, diphtheria).

During the metastasis of the bacteria there is usually no increase in numbers in the circulating blood, *the latter acting rather as a vehicle* to carry the bacteria to other parts of the body; and multiplication first occurs when the bacteria have come to rest. Nevertheless in certain infections—as, for example, anthrax—*the bacteria increase enormously in the circulating blood*, and in this way act harmfully on the blood itself. Should small blood-vessels become filled by the multiplying bacteria, local disturbances in the circulation may be added to the poisoning effects just mentioned.

If the *bacteria* should be deposited secondarily in the mucous membrane of the respiratory or genito-urinary tracts, *they may multiply within these tracts* and carry on their characteristic pathological processes. In the same manner *they may multiply in the greater cavities of the body*, as the peritoneal, pleural, and subarachnoid spaces. Should a woman at the time of infection be pregnant, there are quite *a number of varieties of bacteria which may be carried to the fœtus* (the bacteria of anthrax, malignant pustule, symptomatic anthrax, glanders, typhoid fever, relapsing fever, pneumonia, and pus-diseases).

The description given above of the course pursued by the different infections can be considered as applying correctly to the typical cases, and there are many infections which run this course (typhoid fever, pyæmia, erysipelas, diphtheria, tetanus, tuberculosis, syphilis, leprosy, glanders, actinomycosis, etc.). On the other hand, there are also many deviations from such a typical course. In the first place, it frequently happens that in infectious diseases which, in general, adhere to the described type, the locality of the inception of the infection is not discoverable, either because no changes have taken place at the point of entry, or because these changes have already disappeared. Such forms are called **cryptogenic infections.** It also happens in many typical infectious diseases that the primary location of the cause of the disease is not recognizable, so that *general disease symptoms occur before any local disease can be recognized*, and the tissue-changes produced later on have more the appearance of a *secondary localization of the disease poison.* This occurs in a number of infectious diseases whose causes are not known, as, for instance, in scarlet fever, smallpox, and measles; while in some infections, the causes of which are known to us, it is not possible to specify the point at which the first multiplication of bacteria takes place. Thus, for example, in the case of relapsing fever, we only know that at the time of the fever the spirilla are found in great quantities in the blood; the place where they multiply, however, is not known.

Not infrequently we have a **secondary infection** accompanying one already present. In many cases the association is entirely accidental, while in other cases the anatomical changes set up by the first infection produce a local predisposition to the new invasion. To the first group would belong, for instance, a croupous pneumonia occurring in a patient suffering from tuberculosis of the lungs, while with the second group we would class an infection with bacteria which produce pus and septic intoxication, as occurs in infected wounds, and during the course of typhoid fever, diphtheria, scarlet fever, dysentery, caseous ulcerating tuberculosis, etc. So far as can be judged from the pathological events observed in recent epidemics of influenza in Europe, this disease is also one which predisposes in a marked degree to secondary infections. In certain infections —as, for instance, many forms of suppurative processes—the tissues contain, already at an early stage, two or more varieties of Schizomycetes, a circumstance which shows that in these cases we are dealing with a sort of **association of bacteria—a double infection.**

That decomposition produces substances which are poisonous is a fact which has been known for some years. In 1852 Beck observed that ammonium hydrosulphate, if injected into animals, possessed the septic properties found in pus and sloughs. In 1863 R. Panum secured from putrefied matter a *putrid poison*—i.e., a body which was not destroyed by cooking and steaming. The action of this poison on the body was found to be similar to the action of snake-venom and some vegetable alkaloids, producing in dogs salivation, dilatation of the pupils, diarrhœa, fever, and severe prostration.* Von Bergmann and Schmiedeberg found a crystalline substance in putrefying yeast which they named *sepsine*, and which produced symptoms of putrid infection in animals. By the use of glycerin, Senator, Hiller, and Mikulicz extracted, from decaying tissue-masses, a substance which exerted a similar septic action. Billroth called these poisonous substances *putrefaction zymoids.* Selmi endeavored to characterize all these substances more minutely, and he succeeded in obtaining from different cadavers a number of extracts soluble in ether or in water, which he recognized as fixed bases of alkaloidal character, and which he designated as **cadaveric alkaloids** or **ptomaines.** Gautier, Etard, Zuelzer, Sonnenschein, Béchamp, Schmiedeberg, Harnack, von Nencki, Willgerodt, Otto, Angerer, Maas, and others also found in decomposing tissues the same or similar cadaveric alkaloids, and their experiments with these upon animals showed that in some cases these substances produced no effect whatever, while in other cases they produced poisonous symptoms similar to those produced by curari, morphine, and atropin. Von Nencki (1876) discovered a cadaveric alkaloid (*collidine*) which, as a salt of platinum, crystallized in flat needles. He also produced it in a pure state, and made out its chemical formula. According to von Nencki, Etard, Gautier, and Baumann, and especially Brieger, have studied these ptomaïnes, and the latter has produced a large number of them in a pure state, and has ascertained their physiological action. Brieger, for instance, has extracted from fibrinopeptone a poisonous substance (*peptotoxin*) which produces in animals paralytic symptoms and ultimately death. From decomposing horse-flesh he extracted three substances, crystallizing in the form of needles—namely, neuridine, neurine, and choline, the second of which is markedly poisonous, and, like muscarine, produces salivation, alterations in the respiratory and circulatory functions, contraction of the pupils, and clonic spasms. From fish he obtained, besides neuridine, three other poisonous substances—namely, ethylendiamine, a substance similar to muscarine, and a substance called gadinin. From decaying cheese and glue he obtained the poison neurine, and from decomposed yeast, dimethylamine.

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* See Panum, "Das putride Gift, die Bakterien, die putride Infection und die Septikämie," *Virch. Arch.*, vol. lx., 1874.

The majority of ptomaïnes are not present in fresh tissues, and it is probable from this that they are derived from the breaking up of chemical combinations which are contained in the tissues. Thus, from lecithin, choline is probably derived, and from this is then produced the poison neurine.

Choline and neuridine, according to Brieger, are already recognizable in the fresh human brain.

When the poisonous character of a part of the ptomaïnes was learned from these investigations, there was a tendency to assume that the toxic symptoms observed in infectious diseases are due entirely, or in a great measure, to the substances called toxins. By investigations conducted during the last few years by Roux, Yerson, Buchner, Brieger, and C. Fränkel, it has been established that the **toxalbumins** play a more important part than the toxins, and can therefore be called the *peculiar specific poisons of bacteria*. Of the active albuminoid substances one formerly knew only the enzyms—pepsin, trypsin, ptyalin, diastase—which produce a hydrolytic decomposition into various elements. The actively poisonous albuminoid bodies, the toxalbumins, have only become known through the study of infectious diseases in late years. Brieger and Fränkel are of the opinion that the toxalbumins which produce the poisonous symptoms are formed, by the action of bacteria, from the albuminoids of the juices of the body. Buchner, on the contrary, holds the opinion that they are produced from the cell-contents of the bacteria themselves, and brings forward, in support of this view, two facts—namely, that the diphtheria-bacillus is capable of producing its toxalbumin in urine free from albumin (Guinochet), and that the tetanus-bacillus produces its toxalbumin in a solution of asparagin and animal salts. The toxalbumins and the enzyms lose their virulence in solutions at a temperature of 55–70° C. In the dry state they can withstand much higher temperatures.

It is noteworthy that, after being injected into the tissue of an animal, the toxalbumins do not act immediately, but after some hours, or even after some days. They differ, therefore, in this respect from ordinary poisons.

Should the composition of the blood be altered and the blood and body-juices be infected by the continuous introduction of harmful substances from bacterial colonies, a condition may be produced to which the term **dyscrasia from bacteria** may with propriety be applied. In this connection it should be mentioned that this name, which formerly indicated an alteration in the constitution of the blood and fluids of the body, which was formerly much used, and which played a great rôle in pathology, is employed very little at the present time.

§ 15. The **disease-producing Mucorineæ and Saccharomycetes** belong, as do the Schizomycetes, to the non-chlorophyllaceous thallophytes, and enter into the human organism in the form of inarticulated and articulated, and sometimes ramified, filaments or *hyphæ*, and short oval cells, the so-called *conidia*. These organisms sometimes form peculiarly shaped seed-organs. The individual cells are much larger than those of the Schizomycetes, so that they may already be recognized by the aid of a slight magnifying power. Outside of the body the *Mucorineæ* develop as moulds of various colors on the surface of all sorts of organic substances and solutions, whose carbon compounds serve for their nourishment. The *Saccharomycetes* or *yeast-fungi* are found in fluids containing sugar, and are the cause of their alcoholic fermentation.

The spores or conidia of the Mucorineæ are to a great extent developed in special seed-organs, but they are also occasionally cast off from the ends of the stalks or filaments by a simple process of constriction, these latter constituting a specially resistant type of propagation-cells. Both varieties find their way into the air and may be widely scattered by its currents. In a similar manner the yeast-cells can be carried about in the air, in case any fermentative fluid dries up and the remaining solid product becomes reduced to dust.

As disease producers, the Mucorineæ and Saccharomycetes are much less important than the Schizomycetes, since only a few forms can be reproduced within the human body, and since those which do so multiply always develop only in a very limited area, so that the disease produced remains a purely local one. Finally, they do not produce poisons which are capable of acting upon the entire organism, or upon the nervous system, or upon the blood, but, at most, substances which act only upon the tissues in the near neighborhood of the filaments. They can, therefore, produce only **local infectious diseases.**

The points of entrance for these organisms are in general the same as those for the bacteria. The development of fungi almost always occurs at points which are accessible from without. Very frequently they develop only in the dead material which lies upon some particular part of the skin or mucous membrane, or upon the surface of a wound. Thus the external ear, from uncleanliness, from the presence of cerumen, or from oil dropped into the canal, may become the seat of their growth. They may develop in necrosed portions of lung-tissue, or in dead epithelium and food-débris in the mouth. Through the introduction into the stomach of liquids undergoing fermentation, a further multiplication of the mould may there occur; and, besides, the stomach usually contains a small number of saccharomycetes. The action of these saprophytic growths of moulds and yeast-fungi is in general insignificant, the latter practically *nil*. The changes produced by the yeast-fungi at the spot where they multiply tend to excite inflammation. The local action is increased by the penetration of the filaments into the living epithelium, at which points they play the part thenceforth of a parasitic growth. Under certain conditions the fungi may penetrate into the connective tissues, but even then their extension is limited. Only in rare instances and under peculiar circumstances has the spread of the conidia by means of the lymph and blood been noted. When this happens, however, and conidia are deposited in other organs, they may there develop into filaments, and cause local degenerations and inflammations. But from these secondary centres no further extension takes place.

Their rôle as parasites is most strongly accentuated in the case of a few forms of filamentous fungi (favus, herpes tonsurans, pityriasis versicolor) which are encountered in the skin, for in this locality they develop in the epidermis and its adnexa, in the hair and nails, and cause there peculiar epithelial degenerations and inflammations of the papillæ and corium.

§ 16. The **production of diseases by animal parasites** can most frequently be traced to the fact that the mature parasites, or their larvæ or eggs, are introduced into the intestinal canal by means of the food or drink or by unclean fingers; and this is particularly true of those parasites whose habitat is the intestine or other structures located in the interior of the body—a circumstance which has caused them to be named *Entozoa*. Parasites that live in the outer tissues of the body—namely, the skin—and are consequently called *Epizoa*, either remain only on the outer surface of the skin, or penetrate from without into it. If the parasites pass from the intestine into the surrounding tissues, the condition, according to Heller, is called an *invasion-disease*. Animal parasites produce only local changes; yet they may also induce symptoms of a general disease, especially when they are present in great numbers in the body, and pervade thickly either the blood or certain tissues.

Some of the **parasitic Protozoa** are harmless, inasmuch as they develop in the secretions of the mucous membranes without producing morbid conditions. Other forms, on the contrary, penetrate the living tissues and multiply within the cells, so that localized pathological conditions, characterized by the new formation of peculiar tissues, are produced (see, in Section IX., Coccidia-disease of the Rabbit's Liver and Epithelioma Contagiosum). Certain forms, which probably are to be classed among the Sporozoa, multiply as inhabitants and destroyers of the red blood-corpuscles, and are the cause of the infectious disease which is called malaria. The malarial parasites develop externally to the human body, in the earth of certain localities, and are probably taken into the human body through the respired air. It is not impossible that other infectious diseases—for instance, smallpox—are caused by parasites that belong among the Protozoa.

Parasitic worms (*nematodes, cestodes, trematodes*) dwell in the human body, sometimes fully developed and capable of reproduction, at other times as larvæ; in the first case they are mostly intestinal parasites which live on the contents of the intestine, rarely sucking the blood from the intestinal mucous membrane. There are, besides, worms which develop in other regions—e.g., in the blood-vessels, in the lymphatics, in the lungs, in the pelvis of the kidneys, and in the skin. If they produce either eggs or developed larvæ, these either pass away with the dejecta or reach, through active wanderings or by being carried in the current of the blood and lymph, other organs of the body, and thus complete their first stage of development. In this new locality, however, they do not again reach the reproductive stage, but remain in the larval condition. Further development only takes place when these larvæ reach a new host.

The worms which attain the reproductive stage in man enter as larvæ with the food and drink, having made their first development in animals the flesh of which serves us as food; in some cases, however, they are derived from certain of the lower animals that do not serve as food. Others, again, develop in water or moist earth, or even in the intestinal tract of man, so that the eggs or the embryos, which pass off with the dejections, at once commence to develop again, provided they find an entrance into the human intestinal tract.

The worms which exist in man only in the larval form (as the cysticercus) develop from eggs which have come from sexually mature worms which inhabit different animals. They are taken into the intestinal tract mostly through the media of food and drink; still they may be also, under certain conditions, inhaled in air containing dust which has in it eggs capable of development, whence the eggs get into the intestinal tract and complete the first stages of development.

The intestinal parasites produce generally very little disturbance, though they may irritate the intestine mechanically. Those that suck blood (*Anchylostoma duodenale*) can, if they are present in great numbers, produce anæmia. The parasites which take up their abode in the tissues produce, in their immediate neighborhood, slight inflammation and proliferation of the tissues; but these changes can produce severe symptoms only when the parasites (larvæ of trichinæ) are present in the tissues in great numbers. Some act detrimentally to the parts through the fact that they reach a large size (echinococcus cysts) and thereby crowd aside and compress the neighboring organs.

In general their pathogenic significance depends essentially on their location. A parasite situated in the muscles or the subcutaneous tissues causes slight symptoms, while one located in the eye, the medulla oblongata, the heart, or any vessel, may cause severe complications, and, under certain conditions, death.

Of the **parasitic Arthropoda** (*Arachnida* and *insects*) some come from the outer world, some from infected animals, and some from infected men. Most of them belong to the Epizoa, which have their habitat in or on the skin and accessible mucous membranes (lice, bedbugs, flies, itch-mites), or only occasionally take their nourishment from the skin (gnats, horse-flies, fleas). A few multiply either in the skin (itch-mites) or on its surface (lice). In the internal organs is found only the larva of an arachnoid (*Pentastoma denticulatum*). In so far as the Arachnida penetrate the skin, epidermis, hair-follicles, and sweat-glands, they cause symptoms of irritation and inflammation; the bite of insects that draw blood is also followed by an inflammation in the affected region.

II. Metastasis and Embolism, and their Importance in the Etiology of Lymphogenous and Hæmatogenous Diseases.

§ 17. Injuries acting upon the body from without cause, except in certain cases (overheating of the body, lack of food and oxygen, poisoning by nerve-poisons, etc.), local tissue-changes. Should the local disease be caused by missiles, dust, poison, or parasites, these may at the same time introduce foreign substances into the altered tissues. The consequence of this is that the primary focus of disease very frequently contains portions of the body which have been set free through tissue-changes, and also corpuscular substances which have been introduced from without, both of which are capable, on account of their chemico-physical characteristics, of being taken up by the lymph-currents of the body, or by the blood, and carried to other localities, where they again become lodged. If the substances are insoluble they will be carried along in that form; if they are soluble th of solution, and then either be destroyed or be excreted by the excretory organs, in their original or in a changed form; or, finally, they may be deposited, once more in solid form, in some other organ or tissue of the body.

When a substance which has penetrated into the tissues, or one which has become free in the body, is taken up by the lymph- or blood-stream and carried to other parts of the body, and there deposited, the process is called **metastasis.** If the metastasis occasions a pathological change in the tissue involved, we speak of a **metastatic disease.** Inasmuch as the latter must originate either in the lymph or in the blood, it is correct to speak of it as either a **lymphogenous** or a **hæmatogenous disease.**

As has been seen in the preceding chapter, metastases play an exceedingly important rôle in the pathological processes that occur during life, and yet they are not all of equal significance. The **importance of the metastasis** is dependent rather upon the nature of the transported material.

In the first place, the *size of the metastatic body* influences greatly the course and action of the metastasis, as very small bodies can pass through all the blood-vessels—even the capillaries—while larger bodies can only be transported through vessels the diameter of which when filled exceeds their own diameter. Should one of these bodies in any way enter either the pulmonic or the general circulation and be carried along with the blood-current, its further progress will be stopped when it reaches one of the subdivisions of a vessel which has a calibre too small to permit the body to pass, and then the latter will plug the vessel more or less perfectly. When a somewhat large particle is forcibly thrown in this manner into a vessel it is customary to speak of the occurrence as an **embolism,** and the body that remains fixed in the vessel is called an **embolus** or a **thrombus** (Fig. 2, *b*). The effect of an embolism is generally to stop the vessel more or less completely and to interfere with the circulation; yet there are cases in which the resultant alterations in the circulation are very varied, owing to the fact that at one time either a complete or a partial compensatory circulation may be established behind the embolus, while at another time such a compensation may be entirely wanting (see Section III.). If the compensation be insufficient, or if it be entirely wanting, the tissues supplied by the ramifications of the plugged blood-vessel will either undergo degeneration or will die.

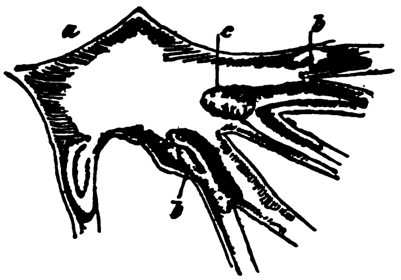

FIG. 2.—Multiple emboli in the branches of the pulmonary artery, after thrombosis of the right auricle. *a*, Arterial branch; *b*, embolus; *c*, embolus, associated with a condition of thrombosis.

The *nature of the transported body* (the embolus) has the greatest influence upon the subsequent events of the metastasis. If it is a small, bland, insoluble body, its action on the tissues will be very slight: if it is soluble and chemically active, it may produce very marked tissue-changes. If it is made up of bacteria capable of multiplication, they can, by increasing, produce a pathological change similar to that which occurred in the original seat of infection. If they are tissue-cells capable of growth and increase, they may induce a pathological growth.

Metastasis may occur in the lymph-channels as well as in the blood-vessels, and this usually takes place in the direction of the normal current; but in exceptional instances it may take place in the direction opposite to the current—that is, a **retrograde metastasis** may occur. In the lymphatic channels such a change in the direction of the current occurs when the normal escape of lymph from the territory involved is hindered by the stoppage of the lymphatics, and the lymph is thus compelled to seek other outlets. A similar condition may be produced in areas supplied by blood-vessels situated at the periphery of the body. Then, again, plugs may be forced back from the vena cava, by blood-waves running in the reverse direction, into the peripheral venous branches. According to the experiments of Arnold upon dogs, foreign bodies (small particles of wheat) which were introduced into the jugular veins, crural veins, and longitudinal sinus of the dura mater, and which were too large to pass through the capillaries, were carried, by a current running in the reverse direction, not only into the trunks, but also into the smallest branches of the veins in the liver, kidneys, heart, extremities, dura and pia mater, and orbits, as well as into the posterior bronchial veins.

If there chance to be an opening in one of the septa of the heart, it is possible that particles circulating in the blood may pass directly from one side of the heart to the other, and so give rise to the condition termed **a crossed** or **paradoxical embolism.**

The transported particles start in the first place from the primary foci of disease, but it must not be forgotten that such a transported substance may a second time undergo transportation; and, further, that in a metastatic centre of disease there may be produced a fresh crop of transportable particles, which afterward can be swept along by the blood- or lymph-current to other portions of the body. There can consequently be produced from one metastatic focus of inflammation other new metastases. Finally, it also happens that diseases plainly dependent upon some contamination of the lymph or blood—and which, therefore, may rightly be termed **lymphogenous** and **hæmatogenous diseases**—are developed without our being able to find the primary centre from which the disease started. As such centres often contain bacteria which can originate only in the outer world, one must suppose that these organisms, which ordinarily produce inflammation at the point of entrance, may under certain conditions enter the tissues, and eventually reach the blood- and lymph-channels, without causing such changes at the point of entrance, and that afterward their presence in these fluids may be discovered—a chain of circumstances which gives color to the belief that *a cryptogenic infection may take place, and that the metastatic disease may assume the appearance of a primary affection.* This can happen not only when pathological changes are entirely absent at the point where the bacteria entered, but also when they may at one time have been present, but afterward entirely disappeared before the time of the examination.

§ 18. The bodies which produce metastases can advantageously be divided into six groups, in which arrangement both the source and the nature of the transported bodies, as well as the effects of the metastases, will be found to have received due consideration.

The first group is made up of insoluble, lifeless substances composed of very small particles, which enter the body from without and which may be called **dust-particles.** The majority of them enter the body by way of the respiratory tract, and pass from the lungs into its tissues. A few may enter the tissues by unintentional or intentional wounds (tattooing). Most frequently they are particles of soot, coal, and stone, while less frequently they are metal, porcelain, tobacco, hair, and divers other dusts. In tattooing of the skin, soot, cinnabar, and other granular coloring-matters play a part.

How the tissues of the organism behave toward these bodies will be described in other places (see Section VI., Chapter III., and Section IV., Chapter IX.). It is only necessary to mention here that these dusts, sometimes in a free state, sometimes within the cells of the tissues, are deposited in the tissues at the point of entrance, or after a time in the lymphatics and lymph-glands. In the latter organs they may remain for a lifetime; but when there is a great deposit the possibility arises of their being transported to remoter spots, this occurrence being likely to take place when the lymph-glands undergo softening by reason of the great quantity of particles deposited in their substance, and excite inflammation and proliferation of the tissues in their neighborhood. As a result of this inflammation the affected lymph-glands are likely to break down and establish a communication with a neighboring vein, and this is especially apt to occur at the hilus of the lung, where eventually the contents of the gland find their way—sometimes immediately, sometimes more slowly—into the calibre of the blood-vessel, and ultimately into remoter parts of the vascular system. According to Arnold, dust in the lung can lodge directly in the wall of the blood-vessel, and thence penetrate even as far as into the intima. Probably particles from a broken-down lymph-gland can enter again into the lymph-stream, and, if not again arrested in some lymphatic gland, may reach the blood-stream. It is also conceivable that softened lymph-glands may break directly into the thoracic duct.

As numerous experiments, some of them very recent, have shown, the dust entering the circulation remains there but a very short time, so that large amounts artificially introduced into a vein are observed to disappear from the circulating blood in a few hours. The greater part is collected in the capillaries of the liver, of the spleen, and of the bone-marrow, and is there found partly within the leucocytes and partly free, in the latter case adhering to the inner surface of the endothelial cells. After a short time there commences an emigration of leucocytes containing the particles of dust out of the blood-channels, so that the dust collects more and more in the tissues, where it is held partly within wandering cells, partly in fixed cells, and in part free for a long while—under certain conditions, even for a lifetime. In the meantime a part is carried, within the lymphatics, to more distant points and there deposited —namely, in the portal and cœliac lymph-glands. Still other dust-cells can, according to the researches of Kunkel and Siebel, reach—through the capillaries of the lungs and the parenchyma of the tonsils, and doubtless other lymphoidal apparatus, as in the intestine—the surface of one of these three cavities, and thence be discharged externally. From the liver they may be discharged by means of the bile. According to observations which one can often make on inflamed organs, the wandering leucocytes are able to transport to the surface in large numbers the foreign particles which lie among the tissues of the lungs, the intestinal tract, and other organs, and in this manner clean the tissues.

The second group of portions of the substance of the body which are occasionally transported from one spot to another by means of the blood-stream is composed of the **remains of tissues** and of **cells of the parenchyma of organs**, in addition to **dead, coagulated, and broken-up blood-constituents.** Among tissue-necroses, the elements which most frequently find their way into the circulation are fat-drops; and this occurs especially when, through trauma or some other pathological process—as, for instance, hæmorrhages—one of the tissues is destroyed. The finding of fat-drops occurs most frequently after the crushing and destruction of fat-tissues, such as are found in the different panniculi adiposi and in the marrow of bones; but fat may also find its way into the circulating blood after destruction of the tissue of the liver. Of the parenchymatous cells, those which most frequently find their way into the blood come from the liver (Turner, Jürgens, Klebs, Zenker, von Recklinghausen, Schmorl, Lubarsch); less frequently are placental cells (Schmorl, Lubarsch) and the giant cells of bone-marrow (Lubarsch) encountered. All of these are generally transported to the arteries and the capillaries of the lung; but they may also, through a retrograde action of the current, be thrown back into the veins; or, through paradoxical embolism, they may find an entrance into the arteries and capillaries of the systemic circulation. Traumatic and toxic injuries and hæmorrhages in the affected tissues give rise to emboli composed of liver-cells and the giant cells of bone-marrow. Placental-cell emboli, in the form of multinuclear giant cells, are observed in puerperal eclampsia, and it is probable that the cramps (Lubarsch), perhaps also the small necroses in the placental villi (Schmorl), are the cause of the metastasis of these cells. According to the researches of Schmorl and Lubarsch, portions of the epithelium of the villi pass into the uterine vein and thence into the circulation. It is possible also that decidual cells enter into the vessels. In pathological conditions of the intima of the heart or the blood-vessels, degenerated endothelial cells, broken-down and degenerated masses of the connective tissue of the intima, portions of the valves, and similar material may enter the blood-stream. Fragments and disintegrated portions of blood-corpuscles may emanate from hæmorrhagic foci or even from the blood-vessels themselves (as in the case where the blood circulating in them has begun to degenerate through the influence of some harmful agency), and in this condition they may form a part of the circulating blood. On the other hand, coagulated masses of blood enter the circulation when a thrombus—i.e., blood coagulated in the vessels (see Section III.)—breaks loose from its attachments, either *in toto* or in fragments.

The fate of the last-named substances is dependent upon their size and physical characteristics. All fragments that are of greater calibre than the capillaries remain impacted in the bifurcations of the artery (Fig. 2, *b*), and generally effect occlusion of the vessel. This usually results from thrombi dislodged from other localities, or from fragments of them. The fat-droplets, on the other hand, generally pass into the capillaries, and some remain there, while others pass through their lumina and only become arrested in some other locality. It is because the fat-droplets occasionally pass into the veins and then into the heart that we find them collected especially in the capillaries of the lungs. They may go, however, still further; passing through the lung, they may reach the capillaries of the major circulation, and thence enter the intertubular and glomerular capillaries of the kidney, and occasionally they are also found to some extent in the capillaries of the brain. Fat-emboli in the capillaries produce noticeable alterations in the circulation only when they are present in great numbers; but when this is the case they can produce œdema at various places in the body (Virchow). Furthermore, fat is destroyed in the progress of metabolic changes.

When transported by means of the arterial circulation, parenchyma-cells remain fixed in the arterioles or capillaries, the stoppage occurring in the former when the liver-cells enter the circulation *en masse*. At the point of impaction their presence can produce a collection of blood-plates associated with a hyaline coagulation, this occurrence taking place in the case of emboli formed of liver-cells. The cells themselves do not multiply, but may remain intact for a certain length of time (according to Lubarsch, three weeks) and then gradually die, when the protoplasm dissolves, and the nuclei swell or shrink and lose their chromatin. In multinuclear cells the dissolving is followed by a clustering together of the nuclei. The locality where fragments of thrombi, or thrombi which have become detached, are arrested is determined by the size of these masses and by that of the vessel in which they happen to be. Inasmuch as thrombi can be produced in the veins, in the right heart, and in the pulmonary arteries, as well as in the veins of the lung, in the left heart, and in the arteries of the body (see Section III.), it is possible for emboli to occur in any of the arteries of the major and minor circulation; and, furthermore, emboli frequently remain fixed at the bifurcation of the arteries, forming *straddling emboli* (Fig. 2, *c*). Through transportation in the reverse direction of the current, emboli may be carried out of the greater veins into the lesser. Defects in the septa of the heart may produce a paradoxical embolism.

Small collections of débris from thrombi, dead red blood-corpuscles or fragments of them, fatty-degenerated and broken-down endothelial cells, etc., in the same manner as happens to particles of dust, either become incorporated into the substance of cells or remain entirely free; in both of which conditions they are quickly removed from the circulation and deposited in the spleen, the liver, and the bone-marrow, where they undergo further changes and are destroyed. Nevertheless the products resulting from the destruction of the blood form colored and colorless deposits in the organs mentioned, and remain there as such for a considerable period of time (see Chapter IX. of Section IV.).

A third group of substances which produce metastases is composed of **living cells** which have originated in **foci of growing tissues**, and are carried to other organs through the lymphatics or through the blood-vessels, into which latter they find an entrance by a direct rupture of the walls of the vessel. This process is observed when a **tumor** develops in some part of the body; and the transportation of living cells from this tumor to other spots in the body, partly by way of the lymphatics and partly by way of the blood-vessels, gives rise to the formation, by a process of proliferation, of **metastatic daughter-tumors** (see Section VII.). Metastasis most frequently occurs in the natural direction of the blood- and lymph-streams; but it may also be effected by *backward* *transportation*, which explains how a tumor which has broken into one of the larger veins of the body produces daughter-tumors in the region drained by another vein. A backward metastasis is frequently seen in the lymphatic system, when closure of one part of the lymph-channels occasions a change in the direction of the current.

As a fourth group we may mention all those processes which are characterized by the entrance of **vegetable and animal parasites** into the circulation. If, under these circumstances, these organisms do not find conditions suitable for their further development, they are quickly eliminated from the blood-current and, under the influence of the metabolic changes, destroyed. But if they are able to reproduce themselves anywhere, they will lead to the production of **metastatic infectious foci**, which are located primarily in the vascular system, but may also force their way from there into the surrounding tissues. When the invading forces consist of bacteria, the secondary infection will have the same character as that of the primary focus (see also Sections IX., X., and XI.). Should an embolus contain organisms which possess the power of inducing necrosis of the tissues, inflammation, and putrid decomposition, there will be produced, along with the embolism and the disturbances in the circulation which necessarily accompany it, suppuration and sloughing; or, in other words, there will be a transportation of the very same process which ran its course at the original seat of infection.

As a fifth group of metastatic processes may be classed together the following pathological occurrences: first, those cases in which **constituents of the human body, having undergone solution**, pass into the circulation, are carried to some other part of the body, and are then **deposited in the new location in a solid form**; and second, those in which **substances are taken up into the body from the outer world in a dissolved condition** and are then **deposited in the tissues in a solid form**. Most frequently it happens that the coloring-matters of the bile are taken up in solution into the blood within the liver, are then distributed to different tissues, and at the same time produce granular or crystalline deposits of *bile-pigment*. Not infrequently, *products from the destruction of red blood-corpuscles undergo solution in the blood-stream*, and are deposited, in the form of drops, granules, and crystals, in the spleen, liver, and kidneys. *Substances derived from the coloring-matter of the blood in hæmorrhagic foci* may also be taken up into the circulation and distributed to various organs.

In rapid reabsorption of portions of the skeleton, *lime-salts* are brought into solution in great quantities, and may produce calcareous deposits in the mucous membrane of the lungs, the stomach, or the kidneys.*

Preparations of silver used medicinally for a long time may produce a deposit of fine *granules of silver* of a grayish-brown color in various organs. The tissues most frequently affected are the connective tissue of the skin, the glomeruli and connective tissue of the medullary substance of the kidney, the intima of the larger blood-vessels, the adventitia of the smaller arteries, the tissues in the neighborhood of the mucous glands, the connective tissues of the intestinal villi, the choroid plexuses of the cerebral ventricles, and the serous membranes.

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* The processes referred to in this and in the next four unnumbered paragraphs probably constitute the author's sixth group.—TRANSLATOR'S NOTE.

The fact that the epithelial tissues and the cerebrum are unaffected shows that there is a selective tendency exhibited by the tissues, and that this selective tendency differs materially from that which is seen in the case of a metastatic deposit of the corpuscular elements. It is well to assume that, for this excretion and precipitation of substances in solution, the chemico-physical character and the functional activity of the tissues which come into contact with the blood containing these substances exert a determining influence (compare Chapter XI. of Section IV.).

If a large amount of **air gains entrance to the right heart,** as may occur from the wounding of a large vein in the neighborhood of the thoracic cavity, or, which happens more rarely, from the opening of the veins (e.g., of the stomach) by an ulcerative process, the air mingling with the blood produces a foamy mass, which the contractions of the heart are scarcely able to drive onward. In consequence of this, the left heart contains little or no blood, the aortic pressure falls, and the individual speedily dies. Should the air enter the right heart only in slight or in interrupted amounts, air-bubbles are formed which may circulate through the entire body. Larger amounts sometimes remain for a time in the vessels of the major or minor circulation, cause their closure, and give rise to disturbances of the circulation which may in turn cause disorders of the nervous and respiratory functions. If this condition does not produce death, the air is reabsorbed after a time.

If the lung-tissue is ruptured by some traumatism or by violent coughing, crying, or vomiting, the air may enter the **connective-tissue spaces** and **lymphatics,** and may extend along these into remoter parts of the lungs, into the pleura and the mediastinum, and even out as far as the skin, thus giving rise to conditions which are termed *emphysema* of the skin, of the subcutaneous tissues, of the mediastinum, etc. Under certain circumstances the air may spread throughout a considerable portion of the subcutaneous lymph-channels and connective-tissue spaces, and when this happens the skin presents a blown-up appearance, and pressure upon it produces a crackling sound.

Arnold believes that the lymphatic glands form a sure filter for dust, and that metastases can only occur after the rupture of a lymphatic gland into a blood-vessel. This opinion, which is supported by the results of numerous experiments, seems to me to be correct for all those cases where the gland-structure is still not too much altered. I think, however, that when the lymph-glands soften, from being overloaded with dust, they may discharge dust-containing, broken-down material through their efferent lymphatics.

As will be shown later (compare Chapter III. of Section VI.), it is an invariable fact that where foreign bodies or dead tissue-masses are present in the midst of living tissues, there wandering cells will be sure to appear, and these, so far as is possible, take up into their substance a smaller or larger quantity of whatever corpuscular materials may happen to be present. This material is then carried further on, especially to the lymphatic vessels and lymphatic glands. Very probably this material is utilized—so far as it is capable of being so utilized—for the nourishment of growing tissue-cells.*

According to Siebel and Kunkel, cinnabar and indigo granules injected into the blood-stream of a frog are rapidly taken up by the leucocytes, and in one or two hours not a granule is to be found free in the blood. At the end of twenty-four hours the granule-containing leucocytes have all passed out of the circulation and lie for the most part rolled together in the capillaries, the largest number being found in the capillaries of the spleen, liver, bone-marrow, and the lungs, while they are found in smaller numbers in the kidneys, and in still smaller numbers in the capillaries of the lungs and of the heart-muscle.

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* Ziegler, "Exper. Unters. über die Herkunft der Tuberkelelemente," Würzburg, 1875; Nikiforoff, "Unters. über den Bau und die Entwickelung des Granulationsgewebes," *Beiträge von Ziegler*, viii., 1890.

Already at the end of two hours a few granule-containing cells and free granules are found in the tissues outside of the vessels, and after a few days they have almost entirely disappeared from the vessels. The granules are then seen partly in the wandering cells, partly in the fixed cells, as well as in the free cells of the splenic pulp (Ponfick) and of the bone-marrow. They may even still be found in these organisms weeks afterward (Hoffmann, Langerhans). Both in frogs and in dogs some of the granule-holding cells find their way into the lumen of the alveoli and bronchioles of the lungs, and are then discharged from the system by these channels. In a short time after the injection a large portion of the granules of coloring-matter are found adhering to the endothelial cells of the hepatic capillaries, while a second portion are found in the leucocytes, which later on escape from the vessels into the tissues. From this point many of them manage to enter the lymphatics of the liver and then ultimately reach the lymph-glands. Finally, a portion of the granules are cast out with the bile, but by what course they manage to enter this fluid is not known. In dogs the pigment granules also collect in the tonsils, and are carried by the leucocytes, into which they penetrate, through the epithelial covering to the outer surface.

According to experiments made on animals by Flügge and Wyssokowitsch,* *non-pathogenic bacteria* introduced into the blood-stream disappear rapidly, while *pathogenic varieties* at first diminish rapidly in numbers, but later increase again gradually. When the tissues are healthy, excrètion through the kidneys does not take place. The non-pathogenic bacteria are collected in the liver, the spleen, and the bone-marrow, and are quickly destroyed. Spores, on the other hand, may remain active for days and even for months.

III. Local and General Diseases, and their Relations to One Another.—Intoxication after Infection, and Auto-intoxication.—Injurious Effects of Diseases of One Organ on Other Organs, and on the General Organism.—Diseases Caused by the Withdrawal of the Functions of Certain Glands.

§ 19. If a local tissue-change is caused by any injurious influence, a **local** or **organic disease** will occur, which is accompanied by a disturbance of function of the affected part or organ. If the injurious influence was exerted from without, the seat of the disease will usually be found at some spot which is easily accessible from without. If, however, metastases have already occurred, then other organs or parts of organs will be found altered at the same time, and we may say, in such a case, that a disease with *multiple localizations* has developed. If the injurious agent finds its way into the juices of the body, without causing any noticeable changes at its point of entrance, although inside the body it induced local alterations, we may speak of the condition as a *lymphogenous* or *hæmatogenous disease*, occurring only at a single spot or appearing at several spots, and involving either a deep-seated or a superficial organ, or part of an organ, as the case may be.

If the injurious substance taken into the system, as happens in the case of many poisons, is carried chiefly to the secreting organs, the kidneys and the liver, and eventually also to the intestine, one may properly speak of the organic trouble which originates in this manner as an *excretory disease*.

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* *Zeitschrift für Hygiene*, i.

All local diseases are characterized first by a disturbance of the function of the organ attacked, and this disturbance, if it be of sufficient force and extent, will make itself known clinically. An intestinal disease caused by the ingestion of caustic poisons, or by the spirilla of cholera, or by any other harmful influence, leads to a train of subjective and objective pathological symptoms, which, through their peculiarities, point to the bowel as the seat of the trouble. If agents capable of giving rise to inflammation are brought to the brain or to the heart, and if they excite in the one or the other of these organs an actual inflammation, there will appear characteristic disturbances of the function of whichever one of these two organs is inflamed. If poisonous substances are excreted by the kidneys, and if, in passing through, they injure the excretory cells, pathological by-products will appear at the same time in the urine, and the experienced physician will be able to judge the nature of the diseased process going on in the kidney from the changes observed by him in the urine.

Many diseases which commence as localized affections retain this character throughout their whole course; and this may be true not only of those which end in recovery, but also of those which end in death. Very often, though, a certain generalization of the disease takes place, or at all events other organs become involved, so that very commonly the picture of disease presented is one of a more complicated character than that presented by a purely localized affection; in a word, the malady presents the character of a **general disease** or of a **disease involving various organs.**

The **effect of diseased organs upon other organs and upon the organism as a whole** varies greatly at different times, and it is not always an easy matter—indeed, at times it is impossible—to explain the relationship between the secondary phenomena and those which belong to the primary disease. If one considers the experience gained from the study of metastasis (§§ 17, 18) and from the observation of the effects of poisons (§§ 9–11), one cannot avoid the conclusion that one of the most important and most frequent processes characterizing the generalization of the phenomena of disease is to be found in the fact that the development of symptoms of disease in other organs owes its origin to the *entrance into the lymph and the blood, not only of corpuscular substances, but also of harmful chemical materials in a state of solution,* both of these products coming from the original local foci of disease. We have already, when speaking of the infectious diseases (§ 14), called attention to this **reabsorption of poisonous substances,** and we here repeat the statement that these **intoxications in infectious diseases** constitute an extremely important feature of the entire morbid process. It is by the action of these poisons upon the central nervous system that a disease receives a certain stamp—recognized by the patient through his subjective symptoms, and by the physician through his powers of observation—which establishes its character as a general or constitutional affection. And then, besides, other organic diseases—for instance, pathological alterations of the heart, of the muscles, of the glands, and particularly of the kidneys—owe their existence to this same deleterious influence, for these poisons affect injuriously the parenchyma-cells of these organs and even the endothelial cells of capillaries.

In infectious diseases these poisons owe their origin to the destruction of the tissue-elements, especially of albuminous bodies, through the instrumentality of the constantly multiplying parasites; or the poisons are secreted by the parasites themselves, and are consequently the product of metabolic changes which are entirely foreign to the healthy human body. This, however, is not the only method of poisoning. There are constantly going on in the body, under entirely normal conditions, certain metabolic processes that yield products which, if accumulated in large quantities in the body, are capable of giving rise to disease. Inasmuch as the organism, without any outside assistance, is capable, through these metabolic processes which take place in its interior, of producing such poisonous materials, we may with propriety designate these poisonings as auto-intoxications.

As a rule, **auto-intoxications** owe their origin to the circumstance that some disturbance occurs in the relations existing between the formation and the destruction or excretion of the harmful products of metabolism, this disturbance resulting in the accumulation of these products in the tissues or in the blood. The commonest form of this disturbance in the relations under consideration is that in which the removal of the products of metabolism is hindered or rendered more difficult. When this is the case the intoxication may be called a *retention-disease*; and yet the cause in such a case may also be an excessive *increase in production.*

If the poisonous products resulting from the decomposition of albumin are retained in the intestine, or if they are formed there in abnormal quantities, they may produce either local changes or general intoxication. For example, under the influence of the bacteria of the intestine they may produce sulphuretted hydrogen from the sulphur of the albuminous bodies in such large amounts that it will find its way into the blood, and the breath will smell of it, or it may be detected in the urine.

If the function of the kidney is so much interfered with that the materials destined for the urine are insufficiently excreted, the resulting retention of these materials may induce a condition of poisoning characterized by a comatose condition, with convulsions and disturbance of the respiration, the whole picture being designated *uræmia.* According to von Limbeck, the retained substances act like a narcotic, and the narcosis commences with dulness of perception and sleeplessness. Fleischer believes that the poisoning causes an irritation of the vaso-motor centre, and that as a result of this irritation a spasm of the blood-vessels is produced, which in turn causes a high grade of cerebral anæmia. It has not yet been determined whether the cause of the intoxication is a single substance or a number of substances, or the products of the decomposition of some retained substance.

If the normal discharge of bile from the liver is hindered by any pathological condition within the ducts or within the liver itself, the constituents of the bile are taken up into the blood, and the condition termed *cholæmia* is produced. The bile-coloring matter, as well as the salts of the bile-acids, are absorbed by the blood, and their presence causes general fatigue, ill humor, cerebral exhaustion, desire to sleep, slowness of the pulse-rate, itching of the skin, and abnormal conditions of hearing and taste. These effects on the heart, the muscles, and the central nervous system are to be ascribed to the bile-salts, which at the same time exert a solvent effect upon the red blood-corpuscles.

The absorption of a part of the contents of the bowel, or of urinary ingredients, or of the constituents of bile, into the lymph or the blood, and their transference to various tissues, constitute the chief foundation of auto-intoxications. There are other substances, however, which originate in the body without the aid of infection, and which may also exert a deleterious influence. Thus, for example, the reabsorption into the circulation, and the transportation to other localities in the body, of the remains of broken-down tissues and disorganized blood produce not only local disturbances, but also symptoms indicative of a general disorder—such, for example, as fever (aseptic fever); and in seeking for the causes of this deleterious influence we are obliged to assume that they consist in part of the unformed ferments or enzyms which develop in the tissues, and in part of the products of metamorphosis which result from fermentation, and also in a measure from some influence exerted by the living tissue-cells.

The term *auto-intoxication* is not used with the same signification by all authors, for many give to it a broader meaning than has been given to it in the preceding paragraphs; some even going so far as to include among the auto-intoxications the poisonings which are caused by pathogenic bacteria. In favor of this interpretation of the term the argument may be advanced that the poisons thus developed also emanate largely from constituents of the body. But it seems to me that such an extension of our idea of what the term *auto-intoxication* should include is not useful or advisable; for, after all, the primary cause of the chemical changes underlying the production of the poison does not reside within the body itself, but enters it from without; or, in other words, the poisoning cannot take place without a previous infection. For these reasons it seems to me more correct to apply the name *auto-intoxication* only to those cases of poisoning which are caused by the products of metabolism within the body—a metabolism brought about either by the influence of the activity of the cells of the organism, or by the activity, within the organism (in the intestine, for instance), of the non-pathogenic bacteria, which are always normally present.

Chronic diseases, which seem to consist in the disturbance of most of the functions of the organism, are very often grouped together under the name of **constitutional diseases.** Samuel includes among constitutional diseases, lasting anomalies of the blood, of the lymph-glands, and of the nerve-substance (neuropathic predisposition), rachitis, osteomalacia, multiple exostoses, weak condition of the muscles, relaxed articular ligaments, etc. Hoffmann * describes, under this heading, anæmias, hæmorrhagic diathesis (hæmophilia), hæmoglobinæmia, rachitis, osteomalacia, chronic rheumatism, progressive ossifying myositis, multiple exostoses, obesity, gout, diabetes mellitus, diabetes insipidus, and Addison's disease. Nothnagel, in his "Handbook of Special Pathology," under the heading of constitutional diseases, leaves out the blood-diseases and only includes rachitis, osteomalacia, gout, obesity, chronic rheumatism, arthritis deformans, diabetes mellitus, and diabetes insipidus. From these examples one can see clearly enough that the ideas in regard to what conditions should be classed as constitutional diseases are very different. In the case of the above-named diseases we are really not dealing with constitutional anomalies, but with the sequelæ of anomalies or diseases of certain tissues, so that the term *constitutional disease* is very frequently misused. Obesity and gout come nearest to meriting the designation of constitutional diseases.

According to Bouchard, auto-intoxications are caused particularly by leucomaïnes—that is, by the products of beginning retrogressive metamorphosis of the albuminous materials, which, under normal circumstances, through the action of intra-organic oxidation, are used up in the formation of urea, and are then expelled. According to this view, auto-intoxications occur in diseases which are characterized by diminished oxidation energy—as, for example, in gout, rheumatism, many infectious diseases, chronic constipation, uræmia, diabetes, and many nerve-diseases. According to Poehl, the ferment which keeps the oxidation processes of the body at normal height is spermin, a base which is found in a variety of glands—the pancreas, the thyroid gland, the testicles, etc.

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* "Lehrbuch der Constitutionskrankheiten," Stuttgart, 1894.

§ 20. The integrity and normal functional activity of many organs are dependent in a great measure upon the maintenance of the normal function of other organs, and it is necessary for the preservation of the normal condition of the entire organism that the individual organs maintain their proper functions. The general organism cannot be deprived of the function of many of the individual organs for any length of time. In consequence of this interdependence of the individual organs very frequently the **altered function of one organ**—even though no actual intoxication be produced by the disturbance—**has a prejudicial influence on other organs, or even may threaten the entire system.**

The dependence of one organ upon another is shown in an especially striking manner in their relation to the vascular system and the blood.

The vascular system and its contained blood have relations to all the tissues, and accordingly *diminution in quantity and diseases of the blood*, as well as *pathological alterations of the blood-vessels*, very often produce diseased conditions in this or that tissue, or even in the entire body. If the amount of hæmoglobin in the blood is diminished by a decrease in the number of red blood-corpuscles (oligocythæmia), or by some pathological change in the corpuscles themselves, or, finally, if the hæmoglobin be made, by the action of carbon monoxide (§ 10), in a measure incapable of taking up the oxygen from the air, the normal amount of oxygen would no longer be carried to the tissues of the body. Consequently, if the amount of oxygen conveyed to the tissues, under the circumstances just stated, sinks below a certain point, deficient nutrition and its attendant fatty degeneration will result; in fact, in exceptional cases, this deficiency of oxygen may produce death, by causing a paralysis of the nerve-centres.

Should the arteries be closed by *thrombi* or *emboli* (compare § 17 and Section III.), or narrowed or actually closed by *thickening of their walls*, as happens in the arterial disease known as *arteriosclerosis* (see Section II. of Special Pathological Anatomy), the regions supplied by the arteries thus affected become the seat of local deficiencies in nutrition and in oxygen-supply, of *local asphyxia*, and, later, of *degenerative processes* which very frequently end in the death of the tissues involved, and sometimes also of the connective-tissue framework of the organ.

In the cerebrum and spinal cord the alterations in the blood-vessels tend to produce ischæmic softening processes (see Section IV.), which frequently cause paralyses, and not infrequently end in death. In the heart, the changes in the vessels produce diffuse fatty degeneration, or local softening of the heart-muscle, as a result of which the function of this organ is disturbed, or it may even become entirely insufficient. In the kidney the secreting glandular parenchyma, together with a portion of the connective tissue, undergoes necrosis and atrophy, and the loss of these substances produces local or wide-spread shrinkings which are called, according to their size, embolic and arteriosclerotic atrophies.

In the stomach ischæmia of the mucous membrane produces local ulcerations; in the liver and in the muscles it induces atrophy; in short, no tissue can withstand the effects of a long-standing bloodlessness or poverty of the blood. Consequently, narrowing or closing of the arteries by clots or by changes in their walls plays an exceedingly important part in pathology, and is not only the cause of *anæmic necroses* (see Section IV.) and *hæmorrhagic infarcts* (see Section III.), but also of numberless *progressive organic atrophies.* In the production of organic atrophies arteriosclerosis possesses a prominent significance, since it is a very frequent disease with the aged, resulting in tissue-degeneration in various organs. As a result of these degenerative processes, most of the organs attacked contain at a later date cicatrized patches, in which the specific tissue has disappeared, while the connective tissue is increased.

The active participation of the vascular apparatus in all *inflammatory processes* (see Section VI.), the *disturbances of the circulation* through alteration in the blood-vessel walls, the *displacements and changing of the vascular channels* which result in part from the *closing of old vessels by proliferating endothelial cells or by thrombi*, and in part from the *formation of new vessels*, make it appear comprehensible how in all chronic inflammations the specific cells, deprived of regular nutrition, undergo degeneration, and frequently become replaced, but only to a limited extent, by connective tissue. The chronic inflammations of glandular structures make this very apparent, for in these organs proliferation of the endothelial cells of the blood-vessels often results in obliteration of their lumina.

If there is a profuse watery discharge from the *intestines* the body will suffer for lack of water; and if stenosis of the œsophagus or of the pylorus prevents the intestinal tract from habitually receiving sufficient food, or if the stomach and the intestine are no longer able to digest the alimentary materials which are brought to them, and afterward to carry them along into the juices of the body, the organism as a whole will be made poorer in albumin and fat.

If the *heart* is unable to drive out with normal vigor the contained blood, evidences of venous stasis will show themselves in the more remotely situated organs. If the *respiration* is impeded, or in any way rendered imperfect, the composition of the blood will undergo alterations. A collection of fluid in the thoracic cavity results in compression of the lung; interference with expiration while inspiration remains perfectly free gives rise to distention, and, later on, to atrophy of the lung. If a portion of the *lung* has been rendered useless by a chronic inflammatory process, the inspiratory distention of the thorax acts only upon that portion of the lung which is functionally active. The effect of this is to produce first an overdistention of this part of the lung, and eventually a condition of atrophy due to the abnormal stretching of the tissues.

By increase in the size of the *liver* compression is exerted upon neighboring organs; diseases of the parenchyma of the liver are often followed by disturbances in the circulation of blood through the organ, and at the same time by stasis in the area of distribution of the portal vein, together with abdominal dropsy.

Prevention of the outflow of *urine* from the ureters retards the secretion of urine and leads to atrophy of the kidney. A large excretion of albumin in the urine produces a diminution of the albumin in the body. The destruction of large portions of the parenchyma of the kidney is followed by increased arterial pressure in the aorta, increase in the heart's action, and hypertrophy of that organ.

An *increased resistance in the pulmonary circulation*, on account of disease of the lungs, is often followed by dilatation and hypertrophy of the right side of the heart. *Obstacles at the aortic opening* which interfere with the emptying of blood from the left chamber lead to hypertrophy of the left ventricle. Stenosis and insufficiency of the mitral orifice cause backward pressure of the blood in the direction of the right heart. This influence may be counterbalanced by a hypertrophy of the right ventricle, or, if this compensation fails, the back pressure exerts its influence upon the veins of the major circulation.

An oblique position of the pelvis produces curvature of the spine. Stiffness of a joint and inability to use it produce atrophy of the surrounding muscles, this atrophy being due to inactivity.

Diseases of the nervous system may give rise to functional derangements and anatomical changes in every organ of the body—in glands, muscles, skin, bones, lungs, heart, intestines, etc. These changes are due in part to an increase, in part to a diminution or even an arrest, of nervous impulses; they are also due to disturbances in the circulation, and perhaps also to the withdrawal of trophic nerve-influence upon which the tissues are dependent for their nutriment. Destruction of the large ganglionic cells in the anterior gray horns of the spinal cord produces atrophy of the corresponding peripheral nerves and the muscles supplied by them. Paralyzed extremities become atrophied. Diseased conditions in the region of the respiratory and vascular centres induce disturbances of the functions controlled by these centres. Injuries of certain portions of the medulla oblongata, concussions of the brain and spinal cord, the presence of tumors in the brain, psychical affections, and poisonings of the nervous system, cause, under certain circumstances, first a rapid absorption of the hepatic glycogen into the blood, and then a secretion of a saccharine urine. . Irritation of the peripheral nerves may produce abnormal reflex sensations and movements, as well as circulatory disturbances, in other parts of the body. Paralysis of both vagi, or of the branches which are given off by them, and which are called the recurrent laryngeal nerves, may be brought about by inflammatory processes or by pressure on the part of neighboring lymph-glands, etc.; and the condition is one which may be followed by inflammation of the lungs, by reason of the fact that the accompanying paralysis of the laryngeal muscles permits the entrance of foreign substances into the lung during inspiration. Diseased conditions of the cutaneous nerves may cause the formation of inflammatory vesicles (herpes zoster), or even ulceration of the skin itself.

The *trophoneurotic diseases of the tissues* are mentioned in the main text only cursorily, and their occurrence is set forth as only a possibility. This is done for the reason that the relations of the trophic nerve-system to the individual tissues are still imperfectly understood, and the opinions of different authors vary greatly in regard to the dependence of the tissues upon the nervous system. Many authors ascribe to the trophic action of the nervous system a far-reaching influence on the various diseased conditions to which the tissues are liable, and attribute to the motor, secretory, sentient, sensory, and reflex nerves the power of establishing the necessary connection with the nerve-centres. Others attribute the same power to special trophic nerves. Thus, for instance, muscular atrophy, glandular atrophy, bone- and joint-atrophies (especially tabes; compare the section relating to the pathological anatomy of the joints), diverse diseased conditions of the skin characterized by thinning, exfoliation of the epithelium, loss of hair, inflammation, etc., unilateral tissue-atrophies, certain forms of degeneration of the heart and also hypertrophic growths of the muscles, the glands, the skin, the bones, etc., all are attributed to affections of the nerves.

It is not to be questioned that, as the result of disturbances of innervation, there are produced both degenerative and hypertrophic tissue-changes and inflammations; but most probably these are dependent not upon a condition of the tissues caused by the removal of or change in nerve-influence, but much more upon the increased or decreased functional activity of the tissues, or upon injury or inflammation and disturbances in circulation which have developed coincidently with the disturbances of innervation. An example of this is seen in the tissue-disturbances which are observed when the affected parts lose their sensibility.

Many draw their conclusions as to the trophic influence of the nervous system upon certain organs from the fact that the development of the body in many respects is dependent upon a full development of the sexual organs. Later observations on the action of injections of the juices derived from the sexual glands into the human economy make it probable that these glands produce chemical substances whose absorption into the juices of the body has an influence on other organs (compare §§ 21–23). According to the observations of Singer[*] in *urticaria*, which develops in connection with disturbances in the intestinal function, the intestinal putrefaction is increased, which may be recognized by the presence in the urine of indican and ethyl-sulphuric acid. The same peculiarity may be observed in other forms of skin-diseases.

§ 21. When glands cease to perform their functions, or if a part of the function of a gland undergoes some alteration, various diseased conditions may result; and we may explain them by assuming that certain harmful products are retained in the system and undergo absorption (§ 19), or also that certain chemical substances which are of importance to the integrity of the economy are no longer produced. In harmony with these ideas we may establish a **group of diseases which owe their origin to the lack of certain chemical substances which cease to be provided when certain gland-functions are abrogated.**

If the lung be considered as a gland, one may include in this group the *diminished absorption of oxygen*, with all its sequelæ, which is brought about by various pathological conditions of the lung. To this group also belong those disturbances of the digestion which result from the permanent or temporary *abolition of the functional activity of the glands of the stomach*, as a result of which the gastric juice loses its peculiar digestive power on the ingested foods—a power which it owes to the pepsin, the milk-curdling ferment, and the hydrochloric acid contained within it, and which is manifested in such acts as the coagulation of milk by the curdling ferment just mentioned, the solution of albumin and gelatin and their conversion into peptones by means of the pepsin, and the conversion of grape- and milk-sugars into lactic acid. In a similar manner we should place in this same group the disturbances occasioned by the *suspension of the secretions of the accessory special glands of the alimentary tract.* Thus, by the cessation of the production of the salivary secretions in the mouth, the action of the ptyalin, which changes starch into sugar, is arrested; by the cessation of the pancreatic secretion, the peculiar effects which it is capable of producing are not accomplished (the following are the effects in question: by means of a diastatic ferment it changes swollen-up starch into dextrine and sugar; it emulsifies softened and fluid fats, partly separating them into glycerin and fatty acids; through the contained trypsin it dissolves albuminoid bodies and gelatinous tissues, converts them into peptones, and then splits them up); and, finally, by the abolition of the biliary supply, the antiseptic action of the bile in the intestinal canal is arrested.

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[*] *Wien. Klin. Wochenschr.*, 1894.

Finally, the diminution in the amount of urea formed in severe diseases of the liver-parenchyma should not be overlooked.

It has been only within the last few years that the significance of the partially recognized disturbances in the functions of the pancreas, of the thyroid, and of the suprarenal capsules has received due consideration. These glands probably produce a secretion the admixture of which with the blood and the juices of the body is necessary for the preservation of the integrity of the organism. Consequently their absence causes peculiar diseases, which are known as *diabetes*, *cachexia thyreopriva*, *myxœdema*, *cretinism*, and *Addison's disease*.

Diabetes is a disease characterized by the presence of a large amount of grape-sugar in the urine (glucosuria), accompanied by a marked increase in the total amount of urine secreted (polyuria), often also by the pathological increase of acetone and by the excretion of aceto-acetic acid and β-oxybutyric acid in the urine. At the same time grape-sugar and the acids just named are found in the blood, and frequently diminish its alkalinity. When the blood of these patients contains a large proportion of acids, headache, a feeling of anxiety, delirium, faintings, and finally arrest of consciousness (coma diabeticum) are apt to develop, and these conditions are probably attributable to intoxication by acids (Stadelmann, Minkowski).

The presence of sugar in the urine may be due to the fact that too much sugar has been taken into the body, so that a portion has entered the urine unchanged (alimentary glucosuria). Glucosuria may also occur in consequence of injuries to particular parts of the medulla oblongata (puncture of Bernard), or as the result of disease in the cerebrum (softening, epilepsy, mental affections, severe psychical derangements, tumors, parasites), or of some form of poisoning (carbon monoxide, curari, morphine, strychnine, amyl nitrite, nitrobenzol), in which the liver probably gives up its glycogen into the blood more rapidly than normal, so that a hyperglycæmia is set up.

Finally, glucosuria may occur when the kidneys are unable to hold back the slight amount of glucose which is normally present in the blood, a phenomenon which may be produced experimentally by the administration of phlorrizin (von Mering).

These alimentary, neurotic, and toxic glucosurias are, however, to be distinguished from the ordinary diabetes in that the cause of glucosuria is to be sought not in an increased conveyance of sugar into the blood or a pathological excretion of sugar contained in the blood, but rather in the fact that the diabetic patient is unable to decompose sufficiently the carbohydrates, and especially the dextrose, while the sugars which turn polarized light to the left (levulose and inulin) usually can be oxidized, if not entirely, certainly in greater amount than dextrose. In most cases, also, the power to form fats from the carbohydrates is lessened; yet there are cases in which this function is intact, and the sugars are stored up in the body as fats (diabetogenous obesity).

According to the investigations of von Mering and Minkowski, which have been confirmed by different authors (Hédon, Lépine, Arthaud, Butte, Gley, Thiroloix, Harley, Capparelli), this loss of power in the organism to oxidize the sugar brought into the body, or to store it up as glycogen or fat, is to be explained by a *weakened functional action of* *the pancreas.* This conclusion is drawn from the fact that, after the total extirpation of the pancreas in dogs, a severe, and after a few weeks fatal, diabetes is produced, which is characterized, as diabetes is in the human subject, by polyuria, polydipsia, hyperglycæmia, glucosuria, a diminution of the glycogen in the tissues, and occasionally also by the existence of active destruction of albumin, by emaciation, by excretion of large amounts of acetone, aceto-acetic acid, β-oxybutyric acid, and ammonia, and by the appearance of a comatose condition. In support of the supposition that there is a definite relation between the disturbance of the pancreatic function and diabetes, we find in certain cases of this disease that the pancreas has undergone some alteration—that is, it is atrophied or degenerated; it should, however, be borne in mind that the anatomical examination often fails to disclose a pathological condition of the pancreas, so that we must content ourselves with the belief that the anatomical alterations which may underlie the functional disturbance of this organ are not sufficiently well marked for us to be able to demonstrate them.

A precise explanation of the causal relations existing between diseases of the pancreas and diabetes cannot be given at the present time; yet from the foregoing experimental researches we may deduce the hypothesis that the pancreas yields a substance to the juices of the body which enables them to destroy the glucose, which power is lost after destruction of this gland. Likewise, an explanation cannot be given of the increase in the destruction of the albumins, and the attendant destruction of β-oxybutyric acid, aceto-acetic acid, and acetone. As these substances are not always found in artificially produced pancreatic diabetes (Minkowski), it would appear that they have no direct connection with the excretion of sugar, but should be considered rather as constituting a complication of diabetes (Minkowski). They may also accompany other diseases (poisonings, carcinoma, derangements of digestion), and are not always to be found in cases of diabetes.

The appearance of *diabetes* after the total extirpation of the pancreas furnishes evidence that the pancreas has an especial function which is of the greatest importance in the normal consumption of sugar in the organism. Lépine is of the opinion that there is in the blood a glycolytic ferment which is derived directly from the pancreas, and that, in diabetic patients and in dogs from whom the pancreas has been removed, the cause of the mellituria is to be sought in a decrease in the amount of this ferment. According to Minkowski, Lépine's experiments are not sufficient for the support of this theory. A satisfactory explanation of the genesis of pancreatic diabetes cannot be given at the present time.

If we remove only a part of the pancreas of a dog, no diabetes occurs, or at least the separation of sugar is much less than after total extirpation of the organ (Minkowski). In dogs under whose skin a portion of the pancreas has been ingrafted diabetes is not produced, even when the gland has been completely extirpated (Minkowski, Hédon); it recurs, however, as soon as the implanted portion is removed.

According to Minkowski, there is no direct relation between the secretory functions of the pancreas and those which aid in the assimilation of sugar.

According to von Mering and Minkowski, poisoning by phlorrizin produces in man and in most animals a marked glucosuria, and symptoms similar to those seen in diabetes may be produced by a continuous administration of the poison. Since the cause of the pathological excretion of sugar lies in the kidney and thus represents a washing out of the sugars from the organism, the phlorrizin diabetes cannot be identified with the ordinary diabetes—that is, the pancreatic diabetes as found in man. In dogs in which diabetes has been produced by extirpation of the pancreas, phlorrizin produces an increase in the amount of sugar excreted (Minkowski).

§ 22. **Cachexia thyreopriva** is a peculiar disease which is *produced by the loss or decrease or suspension of the function of the thyroid gland*, these conditions resulting either from defective development or from pathological changes in the gland. To Kocher belongs the honor of having discovered the cause of this disease, he having observed that it followed the total extirpation of the thyroid gland. Numerous clinical observations and experimental researches which followed this discovery have confirmed the fact that the presence of thyroid tissue is necessary for the maintenance of the integrity of the organism, and that the body, especially during its growth, requires a thyroid gland capable of performing its functions in a normal manner. Probably this gland produces a substance that serves a useful purpose in the metabolism of the body; it is also possible that it changes or destroys deleterious substances circulating in the blood.

According to experimental and clinical observations, the total extirpation of the thyroid gland produces in man, as well as in animals, after a very short time, severe morbid symptoms, which are characterized by the appearance of convulsions and cramps, and finally by palsies of the muscles, so that the condition has been called **thyreoprival tetany.** Young animals and the carnivora are especially sensitive, and dogs die mostly in a short time after the total extirpation of the thyroid.

If the loss of the tissues of this gland is borne fairly well at first, as occurs in human subjects, then after the lapse of months, or perhaps even of years, peculiar disturbances of nutrition begin to show themselves. At first these consist of a feeling of weakness and heaviness in the limbs, sensations of cold, often accompanied by pains and transient swellings of the limbs, and decreased mental activity; then, later, a cachexia, accompanied by anæmia, manifests itself, and at the same time pale waxy swellings of the skin, especially of the face, appear, and there is a noticeable diminution of mental power, together with a decrease in muscular power; and, finally, the termination of these conditions is apt to be death. The removal of the thyroid gland in childhood produces disturbances in development, and may prevent either entirely or partially the growth of the bones in their longitudinal axes.

In thyreoprival tetany the body-temperature is raised; in the cachexia it is lowered.

Pathological functional changes, as well as total extirpation of the thyroid, may produce pathological conditions of the body, and both experimental and clinical observations tend to show that **myxœdema** (Ord) is a disease which is specially dependent upon changes in the thyroid gland. Myxœdema is a condition in which the external appearance of the patient reminds one of the thyreoprival cachexia; there is the same peculiarly pale elastic swelling of the facial skin, which does not yield to the pressure of the finger, and which may also be accompanied by similar pale and dry swellings in other parts of the body. Later on, there is a decrease in intellectual power, which shows itself in an increasing difficulty in thinking and acting, also in dulness of tactile sensation, in retardation of muscular reaction, and in the monotonous, nasal character of the voice. Finally, marked general weakness and often symptoms of actual mental derangement appear, and the fatal termination occurs under manifestations of increasing cachexia, anæmia, and coma.

So far as may be judged from the clinical and anatomical facts observed in patients affected with this disease, it is highly probable that **cretinism**, or rather the alterations in the structure and functions of the body which characterize this disease, is also dependent upon disturbances of the functions of the thyroid gland. Thus we know that in cretinism there is always degeneration of the thyroid gland, which may manifest itself in an enlargement of the organ, together with a certain amount of alteration of its structure (goître), or in a contracted and atrophied condition of the gland. The fact should also be stated that cretins in their general aspect remind one of those individuals whose growth has been stunted through a thyroidectomy having been performed upon them during childhood. The longitudinal growth of the hollow bones is more or less imperfect, while the soft parts are relatively well developed. The different portions of the body are unequally developed. The head, for example, is relatively large; the abdomen and neck are thick; the root of the nose is depressed, while the nose itself is broad and stumpy; the skin, especially of the face, is pale, flabby, wrinkled, and puffy, as if œdematously swollen. The mental faculties are always feeble, sometimes markedly so. The power of speech and of understanding words may be entirely absent; and only those cases of cretinism which are but slightly marked are capable of performing work of any kind.

Since cretinism appears to be an endemic disease in certain regions, it is reasonable to suppose that an unknown local miasm, probably taken into the system in the drinking-water, acts with a degenerating influence upon the thyroid gland during the time of bodily development, and injures the entire organism by disturbing the function of this gland. We have, then, a miasm the action of which produces the same effects as an operative removal of the gland; and since we call this action *epidemic cretinism*, we might also term cachexia thyreopriva *operative cretinism*. In addition, we might add myxœdema to the cretinisms, and term it a *sporadic form*, in contrast to the epidemic.

The great importance of the thyroid gland for the nutrition of the body, the cerebral functions, and the growth of bones, can no longer be doubted, after the numerous clinical observations and experimental researches which have been made (see the works of Horsley, Hofmeister, and de Quervain, in which are to be found summaries of the literature of the subject). Regarding the mode of action of the thyroid gland there are, however, many opinions. It is a striking fact that very small remnants of the thyroid tissue suffice to prevent the evil effects of extirpation, and that the implantation of small portions of thyroid tissue, provided they continue to live in their new surroundings, exerts a curative influence upon tetanilla strumipriva and cachexias trumipriva (Vassale, Gley, Christiani, Leichtenstern, Hofmeister, and others). The same results have also been obtained by subcutaneous injections of the juices derived from the thyroid of an animal, and by administering portions of the gland as food. Hofmeister asserts with positiveness that, in cases like those which have just been enumerated, the thyroid gland contributes to the juices of the body a chemical substance indispensable to the organism.

As further corroborative evidence of the fact that cachexia strumipriva and myxœdema are closely related, we may mention the fact that in myxœdema the existence of degeneration of the thyroid gland has several times been demonstrated. That the clinical manifestations and the pathological changes observed in the two diseases are very similar is a well-known fact. But a still more striking evidence of the dependence of myxœdema on disease of the thyroid gland is furnished by the fact that either the prolonged use of subcutaneous injections of thyroid-gland juice, or the habitual feeding of portions of the gland to the patient, exerts a strongly curative effect upon myxœdema (Murray, Vermehren, Ord, Hellier, Kocher, Beadles, Laache). If the supposition be correct that endemic cretinism is dependent upon degeneration of the thyroid gland, one may hope that this disease, if taken at its inception, may be cured by the suitable administration of thyroid tissue.

Very few characteristic post-mortem lesions are found in persons who have died from cachexia strumipriva or from myxœdema. The central nervous system shows no noteworthy changes, either in tetany (de Quervain) or in cachexia (Langhans, Hofmeister). In the year 1892 Langhans and Kopp described peculiar changes in the peripheral nerves. The conditions which they found are the following: single or multilocular vesicular cells (derived from the endoneurium) in the lymph-spaces of the endoneurium; next, peculiar flat or cylindrical or spindle-shaped bundles of fibres, changed in part, in the centre, to a hyaline mass; finally, on the inner surface of the perineurium, blood-vessels having a thickened homogeneous or concentrically striated adventitia. The importance of these discoveries in cachexia thyreopriva is, however, questionable, since Weiss has found the same condition in healthy dogs upon whom the extirpation of the thyroid had not been performed. According to Hofmeister, the kidneys and sexual glands show degenerative changes.

The most remarkable of the characteristics shown after removal of the thyroid in early life, or after it has become diseased at an early period, is the arrest of the longitudinal growth of bones, dependent upon some disturbance of the process of endochondral ossification. According to Hofmeister, a similar arrest may be produced artificially by operation on rabbits. Another thing worthy of note is the fact that, according to the researches of Rogowitsch, Stieda, and Hofmeister, removal of the thyroid in young rabbits produces enlargement and a peculiar alteration of the hypophysis cerebri.

The assertion, thought to have been established by oft-repeated experiment, that rabbits after extirpation of the thyroid do not have tetany, is, according to the investigations of Gley, which Hofmeister has confirmed, based on an error, arising from the experimenters having overlooked the fact that the rabbit always possesses supernumerary thyroid glands. If these are also removed, along with the regular glands, rabbits—like the majority of carnivora operated upon—die from tetany.

§ 23. **Addison's disease** is a peculiar affection which ends in death after a course, on an average, of two years, and which probably is produced by some alteration of function in the suprarenal capsules. Its most noticeable characteristic is the appearance of a light-yellow-brown to dark-brown diffuse and spotted pigmentation of the skin, which first shows itself in exposed portions of the skin, as well as on the areas usually pigmented, then on the remaining superficial portions and on the mucous membranes of the mouth (melasma suprarenale). Already, before the recognizable beginning of the disease or before the pigmentation of the skin, there occur loss of appetite, nausea, pain in the epigastrium, diarrhœa, and constipation—all of them symptoms of disturbance of the gastric and intestinal functions. Then, later, these are followed by muscular weakness, and finally also by manifestations on the part of the nervous system, such as asthenia, fatigue on slight exertion, headache, dizziness, faintings, epileptic seizures, and a comatose condition.

According to the comprehensive statistics compiled by Lewin, alterations of the suprarenal capsules are found in eighty per cent. of all typical cases of Addison's disease. Most frequently these organs are found to be changed into a caseous or a partly cheesy and partly fibrous mass.

Other lesions which might be called characteristic of Addison's disease are wanting. It can hardly be doubted that the disease of the suprarenal capsules holds a causal relation to this particular disease, so that one may describe it as a *suprarenal cachexia.* In what manner, however, the complete loss of the function of the suprarenal capsules, or simply some modification of their power, produces the injury to the organism, cannot be explained at present. It is not improbable that the suprarenal capsules produce, in a manner similar to that which has been observed in the case of the thyroid gland, a substance which is necessary to the organism. Possibly poisonous substances are also destroyed by the action of the suprarenal capsules.

In the same category with the pathological conditions which result from the withdrawal of a glandular function are to be classed the abnormal symptoms in the growth and functions of the body which are produced by **castration**—i.e., the removal of the sexual glands. If the ovaries are removed from a woman after puberty the changes which occur are referable only to the organs of generation: menstruation ceases, and the uterus atrophies; and yet there are cases on record in which it was observed that changes occurred in the production of adipose tissue and the growth of hair, and also in the general temperament. If the ovaries are removed or destroyed in childhood the growth of the body approaches that of the male; the muscles are strongly developed, the changes in the pelvis do not take place, and the development of the breasts ceases.

Castration in a man produces no marked change in the development of the body. If, on the contrary, boys are castrated the development of the body simulates that of woman. An increased amount of fat is stored up, especially on the abdomen, while the muscular structure is only feebly developed. The external genitalia remain small, and there is no development of either beard or pubic hair. The larynx remains small, and the voice is childlike. The mental powers are devoid of strength or energy.

In castrated stags the antlers are not developed; in cocks the growth of the comb is arrested.

How the *extirpation of the sexual glands* affects the entire body has not been determined with certainty. It is generally supposed that, by means of this operation, the trophic influence which is exerted upon the tissues by the sexual glands, through the nervous system, is withdrawn. It is, however, very improbable that the sexual glands exert such a trophic influence through the nervous system, and the supposition, corresponding more closely to the actual circumstances, must rather be that there is produced in the sexual glands during development a chemical substance which exerts a definite influence upon the growth and development of the body.

According to the opinion of Brown-Séquard, all glands produce a peculiar secretion within themselves, and they contribute substances to the blood which are useful to the organism. He ascribes to the juice of the generative glands a special, exciting, tonic influence upon the organism. According to Poehl, the active principle found in these glands is *spermin,* a base which is present in many glands (thyroid, pancreas, ovaries, spleen), and which, through its catalytic action, is able to restore the oxidizing power of the blood, whenever, through any cause, it becomes reduced below the normal, and to *promote* the so-called *intra-organic oxidation.*

The literature of *Addison's disease* is unusually rich (see works of Averbeck, Alexander, and Lewin), but nevertheless the very numerous clinical and experimental observations have failed to make clear the genesis of the disease, and the precise importance attaching to the suprarenal capsules in the human and animal organisms. Since in some cases of Addison's disease no lesions are found in the suprarenal capsules, the attempt has frequently been made to refer the disease to other localized pathological lesions—as, for instance, of the sympathetic nerves and ganglia; but the conditions found up to the present time do not justify such a deduction. That there have been found in a few cases, even when correctly diagnosed, no degenerative lesions of the suprarenal capsules, cannot be used as an argument against the pathological importance of the degeneration of these glands in the etiology of Addison's disease, since an apparently normal suprarenal capsule may have performed its functions in an abnormal manner.

According to the experiments of Tizzoni, pathological conditions similar to those seen in Addison's disease can be produced in rabbits by the destruction of the suprarenal capsules: as, for example, abnormal pigmentation of the mucous membrane of the mouth, loss of strength, epileptic attacks, comatose conditions, and finally death. It is also of interest to note that in cases in which the animals died in consequence of the operation, Tizzoni found degenerative processes present in the spinal cord.

Inflammatory and degenerative changes in the semilunar ganglia and in other parts of the sympathetic system, and also in the intervertebral ganglia, have been found frequently in Addison's disease, and have lately been more fully described by Fleiner. They can be explained upon the hypothesis of an extension of the inflammation and degeneration from the suprarenal capsules to these points. To conclude from this that Addison's disease is dependent upon a lesion of the sympathetic nerves, and not of the suprarenal capsules, is not sufficiently well founded, since the suprarenal pathological alterations are constant, while those of the nerves have been found in only a few cases.

Alexander found that the suprarenal capsules contain a good deal of lecithin, and he is, for this reason, disposed to believe that the disease of the suprarenal capsules is due to the fact that this substance, which is also present in a relatively large quantity in the central nervous system, is no longer produced.

Abelous and Langlois, who performed experiments upon guinea-pigs by removing the suprarenal capsules, conclude from their researches that, by means of a poison which they produce, the suprarenal capsules modify or destroy a poison that originates in muscles.

Manasse found, in preparations that were removed and placed in a chromic-acid solution while they were still at the normal blood-temperature, that the cells of the suprarenal capsules are in most intimate relation with the veins, reaching out into their lumen, and that in the vessels, but especially in the veins, a peculiar hyaline substance is found, which by the chromic-acid solution is colored brown, in much the same manner as are the surrounding parenchyma-cells. It is therefore possible that from these cells a peculiar substance is furnished to the blood. It should be stated, furthermore, that this substance is also found in arteries. It cannot be demonstrated in alcoholic preparations.

IV. Fever and its Significance.

§ 24. When disease of an organ assumes a constitutional character, or when a disease manifests this character from the very beginning, there is seen very frequently a peculiar combination of symptoms which is called **fever.** It is particularly in the infectious diseases which run their course with toxic symptoms that fever plays an active part. The characteristic mark of fever is the *increase of bodily temperature;* yet other symptoms usually accompany it, as, for example, *increased frequency of the pulse, disturbances in the distribution of the blood,* and *alterations in the interchange of gases in the lungs and in the excretion of urine.* There is usually also a subjective feeling of being ill; and yet it does not form a necessary part of the symptomatology of fever, but is rather the special effect of the infection when associated with symptoms of poisoning; the infection occurring either at the same time with the feverish increase of temperature, or a little before it, or even after it.

The study of the healthy individual teaches us that, in spite of changes in the surrounding temperature and in the external conditions (Jürgensen), the bodily temperature maintains a mean height of 37.2–37.4° C. (98.8–99.3° F.). The normal variation in thermal condition between morning and evening is 1.0–1.5° C. (1.8–2.7° F.), the evening temperature being the higher of the two.

The raising of the temperature of the body above that of its surroundings is produced by chemical changes occurring in the organism, especially in the muscles and glands; so energetic, indeed, may be this process that a rise of 1° C. (1.8° F.) may be obtained within half an hour. This phenomenon of heat-production stands in contrast to that of heat-dissipation, the latter taking place especially through the skin, the lungs, and the excreta. Both processes—heat-production and heat-dissipation—are governed by the nervous system, and it is such regulation of both phenomena that makes possible the normal constancy of body temperature.

On exposure to low temperatures the bodily heat-production is increased (essentially by the action of the muscles), while heat-dispersion is hindered by contraction of the cutaneous blood-vessels and by the inhibition of sweat-production.

On exposure to high temperatures the heat-dissipation is augmented by an increase in the frequency of respiration, by dilatation of the cutaneous arteries, and by an increase in the sweat-excretion.

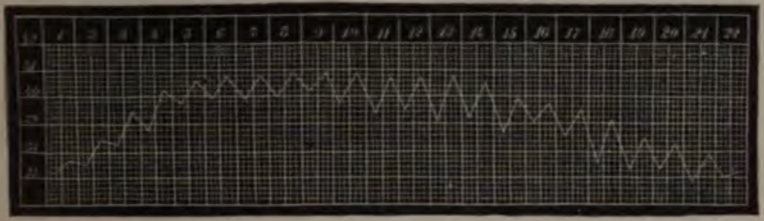

Fig. 3.—Temperature-curve in a continued remittent fever with a slowly increasing and a very gradually decreasing temperature (typhoid fever).

In those conditions which we call **fever** the proper balance between the production and the dissipation of heat is disturbed, the former being excessive; and as a result *the temperature of the body becomes more or less elevated above the normal* (Figs. 3, 4, and 5). Elevations of temperature (taken in the rectum) to 38° C. (100.4° F.) are called *hypernormal;* from 38° to 38.5° C. (100.4° to 101.3° F.), *slightly febrile;* from 38.5° to 39.5° C. (101.3° to 103.1° F.), *moderately febrile;* from 39.5° to 40.5° C. (103.1° to 104.9° F.), *markedly febrile;* over 40.5° C. (104.9° F.) (evening), *highly febrile;* while any temperature over 41° C. (105.8° F.) is called *hyperpyretic.*

Four **periods** may be distinguished in fevers. The first, called the **pyrogenetic** or **initial stage**, or **stadium incrementi,** comprises the time in which the previously normal temperature reaches the characteristic height of the particular disease. This period is sometimes short—from half an hour to two hours in duration (Fig. 4)—and is then generally accompanied by a *chill;* sometimes it is longer (Fig. 3), extending over one or more days, and is then usually unaccompanied by a chill, but in some cases there may be repeated chills.

The second period is called the **fastigium**, or the **acme** of the disease; its duration is very variable, according to the disease, and may be from a few hours to many weeks. The temperature reaches one or more *acme-like crisis-points*, between which are found more or less marked *remissions*.

In the **period of decrease** or **defervescence**, or **stadium decrementi**, the temperature sinks again to normal. If this occurs rapidly, by a sudden decrease in the temperature (Fig. 4), it is called **crisis**; if it occurs gradually (Fig. 5) it is termed **lysis.** The former is usually accompanied by profuse sweating, and in a few hours, or at most in one day or a day and a half, the temperature sinks two or three degrees, or even, under exceptional circumstances, five or six degrees (Centigrade).* In lysis the temperature falls gradually in from three to four or more days, and may be either continuous or intermittent.

Fig. 4.

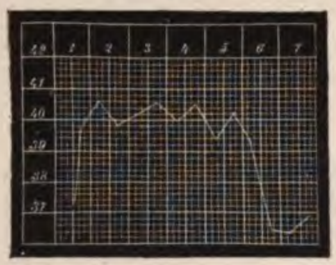

Fig. 5.

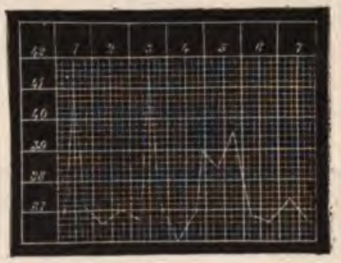

FIG. 4.—Temperature-curve of a continued fever with rapid increase and rapid decline of temperature (pneumonia).

FIG. 5.—Temperature-curve of an intermittent tertian fever (malaria).

The boundary-line between the acme of the disease and defervescence is not always sharply defined, and before the latter sets in definitively, increases in temperature may occur; this phenomenon is called the **critical change,** or **perturbatio critica.** If between the fastigium and defervescence there are days of uncertainty, with occasional changes in temperature downward and upward, we have what is called the **amphibolous stage.** Sometimes there is observed a short period in which, while the temperature is somewhat lowered, it yet remains constantly above the normal; but after a few days it sinks either rapidly or by a gradual decrease to the normal.

In the **convalescent period** the temperature returns again to the normal condition. The heat-regulating function during this time, however, is still imperfect, so that often slight increases and not infrequently subnormal temperatures are observed.

If in the course of a fever the daily variations are small, so that the difference between the maximum and minimum is no greater than under normal conditions, the fever is called a **continuous fever** (*febris continua*) (Fig. 4). If the differences are greater the fever is termed a **subcontinuous fever** (*febris subcontinua*) or a **remittent fever** (*febris remittens*) (Fig. 3), or an **intermittent fever** (*febris intermittens*) (Fig. 5). In the latter condition afebrile periods (*apyrexia*) alternate with periods of high temperature (*pyrexia*), and each *paroxysm* has its period of greatest intensity, or fastigium, and its defervescence. In the infectious disease called **relapsing fever** (*febris recurrens*) there is first a continuous fever, which after a few days falls suddenly; after about one week a second rise in temperature may occur, to be followed, after the expiration of another period of apyrexia, by a third return of the fever.

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* Nine or ten degrees Fahrenheit.—TRANSLATOR.

Many diseases—as, for example, typhoid, pneumonia, measles, relapsing fever, etc.—are characterized by typical temperature-curves, while others—like pleuritis, endocarditis, diphtheria, tuberculosis, phlegmon, etc. —show no typical febrile course.

The **elevation of the body-temperature** in fever is dependent, primarily, upon an *increased metabolism*. The *respiratory interchange of gases* —the giving up of carbonic acid (Liebermeister, Leyden), and the taking in of oxygen (Zunz, Finkler)—*is increased*, a proof that the oxidation processes and the heat-production are increased. At the same time *the excretion of nitrogenous substances in the urine* (urea, uric acid, creatinine) is increased—on the average, 70 to 100 per cent., but under certain conditions to as much as threefold. The destruction of the albuminoid substances in the body is also increased, and this occurs even as early as in the latent period of the fever (Naunyn).

The increased heat-production in fever is accompanied by an *increased heat-dispersion*. Accordingly a patient suffering from fever gives up more heat in a bath than would a person in normal condition (Liebermeister, Leyden). The increase in heat-dispersion does not, however, counterbalance the excess of heat-production. While the *heat-dispersion is only irregularly increased*, the heat-production is kept continuously augmented.

In the initial period the skin is pale, and the cutaneous vessels, in consequence of irritation of the vaso-motor nerves, are contracted; heat-dispersion is slight, and, under certain conditions, may even be less than normal.

Rigors occur in fever when, through the contraction of the peripheral arteries, the amount of blood, and consequently the heat-supply, furnished to the cutaneous nerves is suddenly decreased.

In the second stage of the fever the skin is frequently hot and reddened, and in certain diseases sweating occurs; but the increased heat-dispersion occasioned thereby is, however, not sufficient to reduce the temperature to normal. The increased irritability of the vaso-motor nerves, or the deficient irritability of the vaso-dilator nerves (Heidenhain, Naunyn, Senator), is also present during this period, and, as a result, the skin-temperature, as well as the heat-dispersion, varies considerably. The skin is at times pale and cold, at other times red and hot, and the hands may be cold while the trunk is hot. The centres governing heat-dispersion are therefore acting faultily.

In the period of defervescence the relations of heat-dispersion to heat-production are altered, the former being more active than the latter. The cutaneous vessels become dilated, the skin gives out a great amount of heat from the rich supply of blood circulating through it, and, when the critical fall of the fever occurs, there is usually profuse sweating.

We do not know certainly the **cause of fever**, but we can say this much—that fever is generally *the result of the absorption of a harmful agent into the fluids of the body*. In many cases this harmful agent comes from a demonstrable local source—for instance, from a mass of necrosed and broken-down tissue, or from some centre of erysipelatous and phlegmonous inflammation of the skin. Experimentally, fever may be produced by various procedures—for instance, by the infusion into the circulation of the animal experimented upon of blood from another species, by the injection of vegetable or animal substances which have begun to undergo decomposition (Billroth, Weber), etc. In man we may mention particularly the *infectious diseases* as instances of a fever which is produced by peculiar microparasites which multiply within the body.

It is probable that the microparasites multiplying in the body cause —sometimes directly, and at other times by the production of unformed ferments—an increased retrograde metamorphosis of the tissues, and that at the same time substances are produced which act as *poisons* upon the nervous system. Their action may be supposed to be of such a nature that, on the one hand, through conditions of excitability, the activity of the muscles and glands—and consequently the heat-producing metabolism —is increased; while, on the other hand, by the lessened and disturbed functions of the nerves governing sweating, as also of the vaso-motor nerves, the increase of the heat-dispersion does not keep pace with that of heat-production; and, further, that the organism makes an effort to regulate the temperature, but is no longer able, in consequence of disturbances in the regulating apparatus, to maintain it at the normal height. To what extent the bacteria and the ferments produced by them contribute directly to the elevation of the body-temperature; how far this elevation is caused by the increased metabolism due to irritation of the nerves, and, further, how far it is caused by the disturbance of the heat-dispersion, are questions which cannot be determined; one thing is certain—the causative factor is different in different cases. That, under certain conditions, changes in the nervous system, without infection of the tissue-juices, suffice to cause the production of a feverish increase in the temperature is shown by the appearance of fever in epileptic attacks, in the excitation periods that occur in the course of progressive paralysis, after severe frights, after the passage of a catheter into the bladder, etc. According to the researches made by Richet, Aronsohn, and Sachs, it is possible, in animals, by a prick which passes through the cerebral cortex and strikes the corpus striatum, to produce marked elevation of temperature, with increase in the respiratory interchange of gases and in the excretion of nitrogenous material (Aronsohn and Sachs); and the same phenomena may also be produced by electrical irritation of the same portions of the brain. Nevertheless fevers which are the result of neurotic disturbance are seldom seen, and are overshadowed in importance by those produced by changes in the blood and the juices of the body.

The rise of temperature in fever is usually accompanied by an **acceleration of the pulse**; but still, in some cases, the effect of the elevation of temperature can be so greatly modified by stimulation of the vagus—as, for instance, in basilar meningitis—that the frequency of the pulse is diminished. The pulse is at one time full and bounding; at another, through defective contraction of the heart, weak and without body.

The weakening of the contractions of the heart-muscle is dependent partly on the steadily maintained high temperature and partly on the action of the harmful substances which are produced by the morbid processes, which are peculiar to the especial disease, and which exert an injurious effect upon the muscular or the nervous system.

In feverish diseases the sensation of being ill is usually very pronounced, and the patient experiences a full sensation in the head. In a severe fever there are present disturbances of consciousness, symptoms of excitation and depression, hallucinations, delirium, general apathy, involuntary evacuations, tremor of the hands, cramps (in children), etc. The muscles of the body become weak, and not infrequently they are painful. Digestion is decidedly impaired; the appetite for food is slight; the thirst, on the contrary, is increased; the mouth is dry. There is increased frequency of respiration, and upon the appearance of muscular weakness it becomes superficial. The excretion of urine is usually diminished; the amount of urea in the urine is increased, and that of sodium chloride is decreased.

In a long-continued fever marked wasting of the body is produced, a large part of the albuminous materials of the body and of the fatty tissue being destroyed.

It is difficult to say to what extent these symptoms in individual cases depend upon the increased temperature, and to what extent upon the injury done to the organism by the particular morbid process itself, although most of the nervous disorders may be looked upon as resulting from the infection.

Death is commonly due to insufficiency of the heart, and yet it may be produced by the severity of the infection—i.e., by the changes in the bodily juices, through their action upon the nervous system; by wasting of the strength; and also by an excessive elevation of the temperature —to 43°, 44°, and 45° C. (109°, 111°, and 113° F.). It should, however, be remembered that under certain conditions very high temperatures may be endured for a long time without producing death, and that death resulting after a very high temperature is not always due thereto, but is more frequently to be looked upon as partly or entirely the result of the infection.

The discussion concerning the nature of fevers, which Galen described as *Calor præter naturam*, has within the last few decades been greatly advanced by numerous exact clinical and experimental studies, among the most noteworthy of which are those of Traube, Leyden, Liebermeister, Senator, Naunyn, Herz, and Finkler; and we have learned from them of the changes in metabolism, of the increased consumption of oxygen, of the increased excretion of nitrogenous and carbon compounds, and of the changes in heat-dissipation. If, despite this, we have not as yet obtained a complete knowledge of all those morbid processes which, in any given case, produce a feverish condition, we may attribute the difficulty to the fact that the efficient cause of fever is not something uniform, but may be any one of several things, and also to the fact that the feverish increase of the bodily temperature is not always produced in exactly the same way. The increased activity in tissue-metamorphosis and oxidation in the body is not always produced in the same manner. Then, furthermore, the disturbance in the heat-dissipation, through the radiation from the skin and through water-evaporation, is not always the same; in fact, it changes not only in the course of one febrile illness, but also in the diverse varieties of fever. The part which the nervous system takes in the production of the febrile increase in temperature is not the same in every case. According to Senator, there exists in fevers no harmony between regulation of heat and metabolism. One must therefore suppose that in fever heat is produced by other processes besides those which lead to the formation of urea and carbonic acid. According to Herz, heat is set free by the disarrangement in the molecules of the cell protoplasm—a change which takes place in many cells in fever patients, and which leads to the destruction of the protoplasm. Heat may also be set free by the processes of swelling and coagulation which take place in the cell-protoplasm, while at the same time the diminished activity of the regenerative processes in fevers also necessitates a decrease in the power to retain heat.

A good collection of the ancient and modern theories regarding fever will be found in Rabe's treatise.*

V. The Natural Protective Mechanisms, Protective Forces, and Healing Powers of the Human Organism, and their Action.

§ 25. The human organism is not entirely defenceless against the many harmful influences with which men come in contact during the natural course of their lives; it possesses various forms of **protective contrivances** and **protective forces**, which are capable in many instances of warding off noxious influences, or at least of rapidly counteracting their harmful effects, so that a disease is either entirely prevented or shows itself only as a slight lesion, of much less severity than the decided illness which, according to experience, can be produced by this particular injurious agent. As the kinds of harmful influences are numerous, so are the kinds of protection, and they act at very varying periods—i.e., sometimes even before the tissues have begun to be damaged; sometimes not until such attack has advanced to a certain degree and has begun to spread itself, in part by attacking the surrounding tissues or by sending some of its products to distant spots (metastasis), in part by poisoning the body-fluids or by deranging the bodily functions.

If the environment of the body is relatively cold or relatively warm, the regulating powers of the organism are at once brought into play, increasing the heat-production and heat-dissipation, or diminishing them, as the circumstances demand; so that the body is capable, within certain limits, of protecting itself against the influence of the surrounding temperature. If the functions of the regulating mechanism are defective—as happens, for instance, in consequence of a fit of drunkenness—a man is more liable to die from the effects of cold than under normal conditions.

One cannot speak of special protecting mechanisms against gross mechanical influences, yet it is to be noted that the tissues are able, through their peculiar qualities, to suffer numberless traumatisms without themselves receiving any harm. If small, hard bodies, such as dust-particles, reach the mucous membrane of the respiratory tract or that of the intestines, the *epithelium* forms a barrier to prevent their being taken into the tissue-spaces; and, further, if they are present in a locality where there are ciliated epithelia, these, through the *movements of their cilia*, will keep them moving onward, or they will become surrounded by *mucus* produced by the epithelium and the mucous glands, and in this envelope they will be carried outside the body.

Not infrequently wandering cells come to the outer surface of the mucous membrane, encompass the dust-particles, and carry them away within themselves, in a secretion derived from the mucous membrane. This phenomenon, which is called *phagocytosis*, is observed on the mucous membranes both of the pharynx and of the respiratory tract, as well as in the alveoli of the lung; and epithelial cells can also take part in the same work in company with the wandering cells which come out of the tissue-parenchyma to the surface, and which are derived mostly from the blood-vessels, and also from the groups of lymphadenoid tissue found in the mucous membrane. This peculiar phenomenon is made possible by the fact that the cells can, by the motion of their protoplasm, take up small particles, which, like insoluble dust, exert no injurious influence upon their protoplasm. If these cells laden with dust escape outward, the act of taking up the dust into their substance appears as a useful activity —one which aids in the cleansing of the organs from dust. On the other hand, if these dust-laden cells—as happens particularly in the lung-tissue —pass into the lymphatic channels and are laid up along the sides of the channels or are carried into the lymph-glands—in other words, if a metastasis of the dust-containing cells takes place into the internal organs (see § 8)—then the taking up of dust by these cells appears in a less favorable light, and one can speak of the act as a useful phenomenon only when one is prepared to consider the infiltration of the pulmonary connective tissue and lymph-glands with dust as less harmful than the collection of dust-particles on the inner surface of the alveoli.

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* "Die modernen Fiebertheorieen," Berlin, 1894.

When the particles, either free or contained in cells, reach the *lymph-glands*, they are arrested at this point and stored away in the cells of these glands, so that the lymph-glands may be considered to be trustworthy *filters* which guard the blood and the internal organs from the conveyance of dust to them.

Against the action of poisons the human body possesses but feeble powers of defence. Against corrosive substances the epidermis of the outer skin and the mucus of the mucous membranes afford a certain amount of protection; and there may occur, under certain circumstances, a marked increase in the production of mucus—for instance, in the stomach—whereby the irritating action of a caustic fluid may be markedly reduced. Through the transudation of fluid from the blood-vessels upon the surface of the mucous membrane, a dilution of the corrosive solution may be produced, which modifies its action. On the other hand, the extension of the corrosive agent over a larger surface may thus be produced, and may result in a more wide-spread injury to the tissues.

If the poisonous substances are of such a character that, after being taken up into the juices of the body, they act injuriously upon the blood or the nervous system, a protective influence may be exerted by the organism in part through the action of the kidneys, liver, and intestine, which are sometimes able to *excrete the poison rapidly*, and in part through the occurrence of *chemical changes in the poison itself;* but this sort of protection is effective only when the processes referred to take place before any injury has been inflicted by the poison.

§ 26. The human organism possesses various kinds of **protective mechanisms** and **protective forces against the parasitic infections and intoxications**, and they play a very prominent part in all diseases caused by bacteria. According to their activity, these protective forces may be divided into four groups: the first prevents the entrance of the bacteria into the tissues; the second prevents the unlimited local spread of the bacteria which have already begun to multiply; the third prevents their passage into the blood and their transportation (metastasis) to other parts of the body; the fourth hinders the intoxication or weakens and reduces it to a low degree of power.

For the prevention of the entrance of pathogenic bacteria into the tissues, the latter are provided with those peculiar powers which, as we have already mentioned, are also competent to hinder the entrance of dust; and in the accomplishment of this purpose the *protective epithelial coverings* and the *mucus* play a very important part. In the respiratory tract the *movements of the ciliated epithelium* furnish efficient protection, while in the stomach the *gastric juices are poisonous* to many bacteria. It is certain that many bacteria are not able to penetrate the unwounded external skin or the unwounded mucous membrane without some assistance favoring colonization and reproduction, and that the stomach secretions not infrequently destroy the activity of the bacteria (pneumococci, cholera-spirilla) or even kill them.

It appears, also, not only that the mucus secreted by the mucous membranes can envelop the bacteria in its substance, and in this way hinder their entrance into the tissues, but that, what is more important, the mucus acts upon the bacteria with harmful effect, either through a substance which it contains that is injurious to them, or by producing a culture-medium unfavorable to their growth. It happens thus, for instance, according to Sanarelli and Dittrich, that pus-cocci, cholera-spirilla, and pneumo-cocci gradually lose their virulence in the mucus and die, while diphtheria-bacilli, as it appears, are not injured by the mucus.

Many pathogenic organisms, therefore, may obtain a foothold upon the skin or upon some accessible mucous membrane, or may enter the lungs; but comparatively few among them produce an infection. Investigation has shown repeatedly that in healthy individuals there are found in the upper respiratory tract and in the mouth not only harmless bacteria—i.e., those which cannot reproduce themselves in the human tissues—but also those which can undoubtedly cause disease; as, for instance, cocci which produce pus, or those which are capable of producing croupous inflammation of the lungs. From these facts we are warranted in drawing the conclusion that the bacteria which are found upon the mucous membranes, and have perhaps multiplied at these spots, often die and are carried away without having produced infection. This is probably what happens in the case of the above-named cocci, the tubercle-bacilli, and the bacilli of tetanus; and to this number should also be added the spirilla of cholera, which suffer when in contact with the acid secretions of the stomach. Finally, we may also assume that many of the pathogenic bacteria that are inhaled into the alveoli of the lungs do not reach the reproductive stage, but die.

If the bacteria have succeeded in effecting a lodgment at some spot, and have begun to multiply—it matters not whether they effected a passage through the epithelial stratum without aid from some outside source (as in the case of typhoid-bacilli and cholera-spirilla), or whether they succeeded in reaching the connective-tissue layer by way of some small wound (as in the case of tetanus-bacilli, pus-cocci, the cocci of erysipelas, and tubercle-bacilli)—and if their further progress be characterized partly by local tissue-destruction and partly by a poisoning of the juices of the body, there may be brought into action, on the part of the general organism, certain **counter-influences** *which either restrain the further multiplication of the bacteria, or weaken or perhaps even neutralize completely the poisons produced by them.* The first-mentioned inhibitory influence must naturally be situated in the local surroundings, and depends either upon the vital action of the tissues or upon the action of certain chemical substances.

As has already been mentioned, colonies of bacteria produce local tissue-degenerations, inflammation, and proliferation of tissue—all of which are processes in which the amount and the composition of the fluid which may happen to be at the time in the locality undergo a change; and similarly the cells of the locality also become altered. Inasmuch as, in some of these cases, it is noticed that in the course of the processes just enumerated the bacteria die, and that upon their death the infection often ceases, we may safely draw the inference that the cause of the death of the bacteria is confined to the locality involved.

The prevention of the spread of the bacteria and their destruction, in the spots where they are gathered together in colonies, has been ascribed by many authors to the activity of cells which have collected at the point of infection; and at the same time they have acknowledged that the process termed **phagocytosis**—i.e., the taking up of the bacteria by the cells into their substance—plays a decisive part in this work. According to Metschnikoff and others, the amœboid cells of the body carry on a war against the foreign invaders, and endeavor to overpower and destroy them. Such a manner, however, of characterizing the phenomena of phagocytosis amounts simply to a poetical way of expressing one's self, and does not do justice to the essential facts. Its faultiness consists in their attributing consciousness and will-power to the amœboid cells of the body—i.e., to the leucocytes and the multiplying connective-tissue cells. These attributes, it is manifest, could not possibly belong to these cells. Scientifically considered, the gathering together of the cells at the point involved in the disease, and the subsequent phagocytosis, are simply an expression of certain forces which are natural to the amœboid cells. The latter, therefore, in obedience to these laws of their nature, perform certain definite movements when they are subjected to the influence of mechanical, chemical, or even thermal irritants. We know, from numerous investigations made by Buchner, Gabritschewsky, Leber, Massar, and Bordet, that the motile cells of the body can, by means of soluble chemical substances in certain concentrations of solution, be attracted or driven away, and sometimes injured (see the section on Inflammation), and, further, that the contact with hard bodies can stimulate them into pushing out protoplasmic prolongations.

These phenomena are known as **negative** and **positive chemotropismus** or **chemotaxis,** and as **tactile irritability.** We must suppose that the bacteria multiplying within the tissues act upon the amœboid cells through a chemical substance which they produce, sometimes repelling and injuring, sometimes attracting, and in the latter case affording conditions which are favorable to phagocytosis. This supposition is also in harmony with the actual behavior of the cells in the different local infections, since in one case the bacteria are quickly taken up by the cells, while in another they are left undisturbed.

If one considers *phagocytosis* of the cells, in the infections, in the light of a process natural to the life of the cell, one can then classify it only as *a specific process destined to facilitate the taking up of nourishing material;* and this interpretation would have to suffer only one exception, and that is when certain microparasites, themselves possessing amœboid motion, penetrate by their own movements into the cells.

The result of the devouring of bacteria by cells depends sometimes on the activity of the devouring cells, sometimes on the peculiar properties of the microparasite, and can either result in the death and dissolution of the parasite or in the death of the cell; sometimes, also, the bacteria live quietly in the cells, thus furnishing an example of a symbiosis of the cells with the parasites. In the first case the phagocytosis may prove to be a curative process, in that it hinders the multiplication and spread of the bacteria. In the second and third cases, on the contrary, the phenomena are useless for inhibiting the further dissemination of the parasites; in fact, there are cases (leprosy, and to a certain degree, also, tuberculosis) in which the parasites, finding therein a proper culture-medium, increase within the cells and finally destroy them. If these infected cells remain intact for a certain length of time they may wander into other regions and in this way effect a metastasis.

Phagocytosis acts as a protective agent only in a limited number of cases, yet it is not to be doubted that the phagocytes in certain infections can take up not only dead or dying, but also living bacteria not yet injured by other agents, and can cause their death. If a large number of cells collect in the infected tissues, they may on this account, by filling completely the lymphatics, produce a certain mechanical obstruction to the spread of the bacteria; but the protection thus afforded is frequently insufficient.

If the bacteria, either free or inclosed in cells, pass from the lymphatics into the *lymph-glands*, these act as *filters*, as in the case of dust, and retain the bacteria; still this protection suffices only when the bacteria collected here are hindered in their reproduction and are killed by the influence of their surroundings. The destruction can be fully accomplished here, also, under the influence of phagocytosis; but this is in many instances possible only after the bacteria are weakened or have already been killed. The taking up of living bacteria by the cells does not always give rise to their death; in fact, it is frequently followed by an intracellular multiplication of the bacteria.

More powerful than phagocytosis for the inhibition of the spread of bacteria and other microparasites is the action of certain **chemical substances** found in solution in the tissues. Furthermore, since saprophytic, non-pathogenic bacteria injected into living tissues can be killed in a very short time, we must suppose that there are in the tissues substances which are poisonous to many varieties of bacteria and can cause their death rapidly. Then, again, since many pathogenic bacteria develop only locally—for example, the tetanus-bacilli, diphtheria-bacilli, and cholera-spirilla—and after a certain time die within the infected area, without having spread more widely in the body, so is it very probable that the tissues of the body contain substances which are also poisonous for many *pathogenic forms of bacteria* and prevent their wider diffusion. The phenomena observed in local infections show also that these substances are generated at times in increased amounts, or are augmented in their action by newly produced poisonous substances. It is, further, also probable that the crowding together of cells, which takes place either in the infected area or in the neighborhood, tends to increase the production of these poisonous substances, and may thus impede the spread of the bacteria; nevertheless attention should be directed to the fact that in some infections the spread of the bacteria comes to a standstill (e.g., in erysipelas) in certain places where there has been no crowding together of cells. It is a fact that in many infections the spread of bacteria in the body by metastasis either is entirely wanting (as in tetanus and diphtheria) or at least is quite insignificant in comparison with the local infection, and is followed by relatively trifling changes (as happens, for example, in typhoid fever). Now the explanation of this fact is to be sought not so much in the circumstance that local changes in the tissues have hindered the spread of the bacteria into the lymph- and blood-vessels—for instance, by the production of peculiar chemical substances, or by the introduction of some mechanical impediment such as would result from the building of a wall of cells—as in the further fact that *there are present in the lymph and blood itself forces which are able to injure and weaken the bacteria that have been taken in, or even to destroy them.*

Some investigators have been led to believe that the **hostile action of the blood** upon bacteria depends upon the phagocytic action of the leucocytes, and they support this idea, first, by the fact that one very frequently can recognize, after acquired infection, or after one artificially produced by the introduction of bacteria into the blood, such a phagocytosis; and also by the further fact that bacteria within the blood—very many of them contained in cells—are carried out of the blood-channels and deposited in diverse organs—for instance, in the spleen, the liver, the bone-marrow, and the kidneys—in which they die, or from which they are excreted. These observations, however, do not warrant the conclusion that phagocytosis forms in any way a protection against the spread of bacteria in the lymph and blood, since in those very cases in which the bacteria are not carried off in the blood, the phagocytosis is absent; whereas, on the other hand, an entrance of bacteria into the blood, and their multiplication within the vessels, are very often accompanied or followed by phagocytosis. Here, too, phagocytosis is a secondary phenomenon, which occurs when bacteria or protozoa are present in the blood, and, like bland dust-particles, are not able to hinder their being taken up into the bodies of the leucocytes.

When bacteria are taken up by cells they either die or continue to multiply inside the cells; and which of these two courses they will take depends upon their peculiarities and upon the condition in which they are at the time when they are taken up.

According to the researches which have thus far been made, the power which is able to prevent the increase of bacteria in the blood resides principally in **antibacterial chemical substances** which probably belong to the albuminoid bodies (Buchner), and accordingly are termed *protective albuminoid bodies* or *alexins* (the mycosozins of Hankin). The mode of production and the action of these substances are not known, and can be spoken of only hypothetically. So far as conclusions can be drawn from the behavior of the human and animal organisms in infectious diseases, we may assume that in the human organism there are always present certain protective chemical substances, and that others, on the contrary, are produced only after infection has taken place; so that not until a certain stage in the course of an infection has been reached is an inhibitory influence exerted upon the development of the bacteria by antibacterial poisons. Such an assumption is supported by the fact that many bacteria (typhoid-bacilli, the spirilla of cholera, and pus-cocci) possess their full power of virulence when they are first distributed throughout the body in the blood, but afterward they lose their virulence and finally die.

The protection which the *alexins of the blood* afford the organism is restricted to certain diseases—i.e., to those infections in which the multiplication of the bacteria is confined to a limited area, or in which the transported bacteria have lost considerable virulence. On the contrary, in many infections the degenerative action of the blood upon the bacteria seems to be entirely wanting, or, when it is present, is easily overcome—as, for instance, in those infections in which the bacteria multiply in the blood itself (anthrax), and also in those in which the bacteria, though not increasing in the blood (infections of tuberculosis, lepra, and pyæmia), show no decrease in their virulence after metastasis.

The *protective power* which the organism possesses *against the poisons produced in the tissues by bacteria* is to be found in the possibility of a rapid **excretion of the poisons** by the kidneys, and, under certain circumstances, through the intestines and the skin; and the action of these organs is sufficient, in certain cases, to prevent a fatal poisoning. Besides this, in certain infections there is evidently an antagonistic action on the part of the organism, in the sense that certain poisons are rendered inactive or are actually destroyed by **counter-poisons**, or so-called **antitoxins**, or that the toxins and antitoxins combine to produce non-poisonous substances, or, finally, that the products of metabolism of the tissues protect the latter from the action of the toxins. It is, furthermore, possible that by the spread of bacterial products through the body in certain concentration the tissues can be made immune against the same products, or also against the products of other bacteria (see § 29).

The manner in which the organism can protect itself from infection can be treated of here only in a general way; details cannot be entered into, from the fact that in connection with every infectious disease there are special conditions of which it is important that even a person who is accurately acquainted with the etiological factor in the disease should possess some knowledge. The experience acquired in regard to one infectious disease can be applied only in a limited manner to the explanation of the pathological conditions found in another disease.

In general it should be noted that we are yet far removed from a precise knowledge of the protective chemical substances of the body and their mode of action, and that the opinions which have been expressed cannot lay claim to being anything more than mere hypotheses.

The *antibacterial properties of the blood and lymph* in relation to certain bacteria have been established by the experimental researches of a number of authors. These experiments have shown that the destructive action of a definite kind of blood is exerted only upon certain species of bacteria, and never upon all; and that this action, at the same time, is subject to individual variations.

According to the investigations of Fodor, Petruschky, Nuttal, Ogata, Buchner, Behring, Nissen, Pansini, and others, the blood and serum from dogs, rabbits, and white rats are capable of making the anthrax-bacillus powerless, and even of killing it; yet this action is a limited one, so that after the introduction of a large number of anthrax-bacilli into the blood taken from the blood-vessels, the bacilli after a little time begin to multiply. Defibrinated blood of dogs and rabbits can destroy the cholera-spirillum and typhoid-fever bacillus; it is, however, powerless against various forms of pus-cocci and against proteus; the same statement is also true with regard to the blood-serum. Human blood or blood-serum can cause the death of typhoid-bacilli, diphtheria-bacilli, and the bacilli of glanders, but it has no effect upon the bacilli of anthrax. If the bactericidal properties of the blood are exhausted, then these bacteria grow luxuriously in either blood or serum.

Kruse is of the opinion that the bacteria produce, besides chemotactic substances and toxins, still other injurious substances, *lysins*, which can neutralize the alexins and so render it possible for the bacteria, from that time forward, to go on multiplying.

Hankin believes that the alexins might be produced by the leucocytes, especially by the eosinophilous cells; but it would be difficult to substantiate this hypothesis by actual observations.

Kossel holds it to be possible that the nucleinic acid present in relatively large amounts in the leucocytes plays a part in the destruction of the bacteria.

According to the opinion of Bitter, the bactericidal substance found in organs—that, for example, which one can derive from the lymphatic glands, the spleen, and the thymus gland—is to a certain extent different from that which is found in the blood and serum, and consequently does not originate entirely in the blood. It is certain that the bacteria-destroying power of the blood and blood-serum is not the only protective influence which can resist the spread of an infection or prevent it entirely, and can confer immunity.

According to Emmerich and Tsuboi, the bactericidal albuminoids lose their power on being mixed with alcohol and dried *in vacuo* at 40° C., as also by being heated; they recover it, however, when the dried material is dissolved in water containing from 0.05 to 0.08 per cent. of potassium or sodium at 39° C., and their activity can thus be greatly increased (a thousandfold).

According to the observations of Czaplewski, the anthrax-bacilli which have been taken up into the leucocytes degenerate more slowly within the infected organism than do those which are free in the blood or the tissue-fluids. It appears, therefore, that under certain conditions the cells protect the bacteria which are contained within them from the bactericidal substances in the fluids of the body.

§ 27. The **healing powers of the human body** *are furnished by those functions of life which are fitted to compensate for the derangements and changes produced by disease, and to render harmless or to remove altogether any harmful agent that may still be present in the body.* When portions of tissue are destroyed, the *healing* consists essentially in *the removal of the altered and dead parts, and in the replacement of these by new tissue.*

If from any cause the temperature of the body is abnormally low or abnormally high, compensation is effected by a suitable regulation of the heat-production and heat-dispersion, as a result of which the temperature of the body is once more restored to its normal height. If a portion of tissue is destroyed by a traumatism, the organism can repair the defect either by the production of new tissue on the spot (*regeneration*), or by providing a marked increase in other similar tissues (*compensatory hypertrophy*).

If poisons have entered the body and have produced symptoms of poisoning, there are only two ways in which healing can result—namely, through the removal of the poison by the excretory organs, or through its being changed and made harmless within the body. At the same time the damaged tissues, under the influence of a normal nutrition, again receive a normal organization, and any defects that may remain are in due time compensated for.

In infections the healing processes follow directly on the action of the protective forces; indeed, the action of the latter constitutes the first stage of the healing process. Consequently the protective and the healing forces are in a measure identical. If the alexins succeed in hindering the growth of the bacteria, and then if the weakened bacteria are dissolved and destroyed in the fluids of the tissues or within the cells, the first step in the healing process will have been taken, inasmuch as the *causa efficiens* has been removed. If by the massing together of cells in the infected tissues a protective wall is formed against the spread of the bacteria, or if the latter are retained in the lymph-glands and destroyed, then these phenomena may also be looked upon as processes which usher in the healing. In a similar manner the removal of the poisons or the bacteria which have entered the blood, by way of the excretory organs—the kidneys, the liver, and the intestines—not only acts as a protection against further localization of the bacteria and against increased intoxication, but also makes possible, through the removal of the noxious materials, the restoration of the injured tissues.

In many infectious diseases the healing action of the protective agents already in the body is supplemented by the *appearance on the scene of new substances, foreign to the normal organism, which constitute a sort of counter-poison capable of withstanding the existing infection and intoxication;* for which reason these substances are termed **antitoxins.** These antagonistic poisons are produced either by the cells and the blood—both of which have been altered by the infection so as to perform other life-processes—or by the bacteria themselves; they spread through the body by way of the tissue-juices, and thus form an impediment to the further spread and increase of the bacteria.

These antagonistic bodies act in one of two ways: they either hinder the reproduction of the bacteria and kill them, or they alter and render harmless the bacterial poisons, or they combine with them to produce an inactive, non-poisonous substance. Many things tend to show (cf. § 29 that there are infections in which the bacterial toxins and toxalbumins or the antitoxins present in the body, produce such changes in the tissues that they become immune from, or non-poisonable by, the corresponding infection or intoxication—i.e., they are insensitive to the action of the bacterial products.

The cause of healing in infectious diseases is most frequently referable to the fact that chemical substances produce an antagonistic action against the intoxication, and the bacteria are prevented from any further spread and thus die out. The assumption is also warranted that in many cases the bacteria survive and continue to produce poisonous matters, which, however, remain harmless in consequence of an increased power of resistance, on the part of the organism, to bacterial poisons. This assumption is strengthened by the observations which have been made in connection with the acquiring of immunity from particular diseases (see § 29), also by the fact that pathogenic bacteria which produce acute diseases are present for a long time in the tissues, and reproduce themselves, after the morbid symptoms have disappeared or at least have markedly decreased. In individual cases the theory appears admissible that a lack of proper nutritive material produces the death of bacteria; this being true, perhaps, in the case of localized areas of infection (tuberculosis), in which bacteria remain for a long while inclosed in tissue which is dead and which, with the lapse of time, is undergoing alteration, and from which, consequently, they are unable to escape and find a new source of food.

Emmerich believes that there is in the blood a certain albuminoid body, which is characterized by a deciduous atomic grouping easily capable of reacting, to which he gives the name *immunity-protein,* and which combines with the bacteriotoxins to produce an albuminoid body of complex molecular grouping—the *immunity-toxinprotein.* It is claimed that this substance, which is supposed to be present in the blood and lymph, penetrates into the bacteria, and here is broken up into its original component parts. Then it is further claimed that the bacteriotoxin which is thus set free, acting perhaps with the aid of the immunity-protein, destroys the bacteria.

It has often been assumed that the *fever* present in infectious diseases is a process which favors the destruction of the bacteria, and it is not impossible that in individual cases it exerts such a beneficial influence. Thus, for example, it is easy to believe that a parasitic micro-organism that easily endures a temperature of 37–38° C. (98.6–100.4° F.) may not endure one of 40–41° C. (104–105.8° F.), and consequently that high fever-temperatures would be likely to hinder its powers of reproduction. In general it is safe to assume that there is no necessity of fever for the equalization of the morbid disturbances, and at all events that the harm which it produces is not counterbalanced by any good which may thereby be accomplished. And even in those cases in which the metabolism which goes on during the fever produces upon the bacteria a deleterious influence, it is not permissible to consider this as something useful which should be credited to the fever. One could only say that a portion of the morbid processes taking place in the course of an infectious fever induces the formation of certain products of chemical decomposition which act in an antibacterial manner.

VI. Congenital and Acquired Predisposition.—Idiosyncrasy and Immunity.—The Acquiring of Immunity.—Immunizing Inoculations.

§ 28. It is an old observation that *different individuals are diversely disposed toward external harmful agents.* In a certain number of cases this difference depends upon the *general constitution*—i.e., upon the general condition of the body; in other cases there are *local conditions* that produce these differences in behavior. Furthermore, the differences may be *congenital* and *lasting*, or they may be *acquired*, and are then often a *transient peculiarity* of the special individual.

If an individual is markedly susceptible to the action of a certain disease, this condition is termed a *predisposition* to that particular disease. If an individual shows an especial susceptibility to a particular external influence, which is much more marked than the susceptibility thereto which is seen in the majority of mankind, and so constitutes an individual peculiarity, it is termed an *idiosyncrasy*. If, on the contrary, an individual is insusceptible to the action of an injurious force, so that the symptoms of the disease do not appear even when the individual exposes himself to this particular injurious influence, the condition is termed *immunity*, and, according to its grade, it may be distinguished as a *relative* or an *absolute immunity*.

Predisposition has a great influence over the acquiring of infectious diseases, and also plays a prominent part in the causation of numerous other diseases. In one instance it is founded on general constitutional conditions, in another on those which are simply local; and besides it may be a lasting or a transient phenomenon. Mankind has a strong predisposition to measles, smallpox, scarlet fever, cholera, typhoid fever, malaria, tuberculosis, and syphilis; and consequently, in those cases in which the protective forces against infection that belong naturally to every man prove to be insufficient, an infection would be sure to follow exposure, at least in the great majority of instances. It may also be assumed that the *grade of susceptibility* for these diseases *is not equally great in all individuals*, and that *it varies in the same person at different times.* Thus in epidemics of measles certain children who are exposed to infection escape, and later in life are taken ill during some subsequent epidemic—a circumstance which in many cases can be explained only by the supposition that the individual was for the time but slightly susceptible to measles.

For the acquisition of many infections a peculiar *local predisposition* is often necessary, which is gained by *local tissue-changes*, such as wounds, excoriations, and the formation of ulcers. In such cases, therefore, the disease appears as a **wound-infection.**

To this class belong many forms of suppurations, erysipelas, tetanus, hydrophobia, and, in part, tuberculosis, syphilis, glanders, anthrax, and other diseases; and although any of these diseases may occasionally be produced by infection through intact mucous membrane or skin- or lung-tissue, in the majority of cases a traumatic injury or an ulceration furnishes the required *locus minoris resistentiæ* from which the infection can take its start. Thus, for instance, the suppurative inflammations produced by the so-called pus-cocci are mostly diseases which originate in wounds, excoriations, or ulcers; and in the last case they often represent secondary infections, which follow other infections that have resulted in the production of ulcers. Furthermore, they are frequently encountered in some part of the genital apparatus after parturition—i.e., in tissues which, by reason of the childbirth, are torn or crushed, or, through the rubbing off of the epithelium and the superficial layers of the connective tissue (as in the uterus), are laid open to the invasion of bacteria. Similarly, erysipelas and tetanus are diseases which ordinarily develop from small wounds, and the infection called hydrophobia is almost always caused by the bite of an animal having rabies. Finally, we may also assume that the virus of tuberculosis or syphilis very often enters the tissues only where a local lesion has taken place.

The predisposition to diseases which are not of an infectious origin is manifested particularly in those morbid affections which occur as the result of over-exertion, as exhaustive conditions; and also in those which are the result of temperature variations, such as the diseases due to chilling of the body or to the effects of heat-stroke. But this predisposition may also play a prominent part in still other diseases, as, for instance, in various forms of poisoning. Mental labor and psychical irritations, of which human life is full, can produce illness in predisposed individuals—i.e., in those who have a certain weakness or imperfect resisting power of the central nervous system when subjected to the demands made upon it; while in the majority of men the same amount of work will do no harm. It is well known that the functional capacity for work of the muscles is very different in different individuals, and that consequently many are easily tired; it is also known that many are very susceptible to heat and cold. Illness and death from heat-stroke occur only in a small percentage of individuals who find themselves situated in exactly the same circumstances—i.e., in those who, under the conditions named, are unable to endure the strain laid upon them. By chilling of the entire body, or of certain portions of it, which the majority of individuals can bear without receiving harm, many are made ill, and there are individuals who have an excessive susceptibility to influences of this nature.

The weakened power of resistance to outward influences, and the easy exhaustion from work, constitute, in many cases, an individual peculiarity of congenital origin—a peculiarity which sometimes appears only in childhood and is then outgrown, and sometimes persists throughout life. In other cases it is an acquired state, which shows itself especially in convalescence from severe illness, and gradually disappears. Under certain conditions it may prove to be a permanent sequela of the illness out of which it developed.

Idiosyncrasy in regard to certain injurious influences is generally congenital; at times, however, it is an acquired peculiarity of certain individ[illegible]lf in most peculiar ways. Thus, for example, [illegible] r of salad, produces, in certain [illegible] have an aversion to eating dishes prepared from liver or kidneys, and become ill if they compel themselves to eat of these foods. Still others have a peculiar disease, called urticaria, after eating crawfish, lobster, strawberries, raspberries, morels, or asparagus. The disease is characterized by itchy wheal-formations, characteristic skin-lesions, or abdominal cramps and vomiting. Not a few persons are unable to drink boiled milk without experiencing trouble therefrom. Alcohol, even in very small doses, may in certain individuals produce marked excitation, or even narcosis, or marked vaso-motor derangements. The drinking of cocoa can produce cardialgia and dyspeptic symptoms. Doses of morphine or chloroform that are borne by the majority of men without injury may produce, in certain individuals, severe symptoms or even death. Washing the skin with disinfecting fluids—as, for example, with sublimate or carbolic-acid solutions—in a strength usually borne without trouble, may cause not only local derangements of sensation and inflammation, but also, under certain circumstances, an eczema which spreads over the greater part of the body.

On what, in particular cases, the idiosyncrasy depends is not clear. In many cases we may look upon a peculiar irritability of certain portions of the nervous system as the cause of the symptoms. In acquired idiosyncrasy—with regard, for instance, to the taking of certain foods—psychical factors may play a part.

Immunity, like predisposition, is a peculiarity which plays an essential rôle in the pathogenesis of the infectious diseases, and the term "immunity" is used to characterize the behavior of an individual with regard to infection. If a person is so constituted that the parasites under consideration cannot grow in his tissues, this condition is termed immunity, in the narrow sense of the term; if the peculiarity of the individual is of such a nature that the poisons produced by the bacteria are, for him, harmless and produce no effect, one speaks of it as **insusceptibility to poisons,** and uses this term also in cases where a person shows special powers of resistance when exposed to the influence of other poisons—as, for instance, those which come from the phanerogamous plants or from animals.

Immunity and insusceptibility to the poisons of infections and intoxications are partly congenital, partly acquired, and form, where they have existed from birth, a peculiarity which may belong to all men, or may be possessed by only a few individuals. Man is immune from various infectious diseases that are common to domestic animals—for instance, hog-cholera, symptomatic anthrax, and hen-cholera—while he is susceptible to the infection of anthrax and glanders. So far as tuberculosis and actinomycosis are concerned, he is just about as susceptible to infection as are beeves, sheep, goats, and swine. There is an apparent immunity from scarlet fever in the case of a large number of persons; and even as regards measles, smallpox, cholera, and influenza there exists in many persons a relative immunity. At all events, it happens that only a relatively small percentage of the population acquire scarlet fever, and also that, in regions where cholera and measles appear repeatedly as epidemics, a portion of the population escape—a circumstance which cannot be explained by the statement that these persons did not happen to come in contact with the infective poison which is necessary for the production of the disease, but must be ascribed in part to the fact that their bodies were, at the time the virus entered, not receptive, or at least were only slightly so, so that the natural resistant power of the body was able to prevent the infection. It cannot, however, be determined in these cases whether this immunity was absolute and general, or whether, at the point of infection, there were special local conditions which caused the infection to be suppressed. It is an interesting fact that the escape of an individual who has been often exposed to infection during an epidemic is no guaranty that he possesses a lasting immunity, since experience has shown that infection may take place during a later epidemic or later on during the same epidemic. The immunity may therefore be temporary and at the same time only relative; and it is probable that at certain times a stronger predisposition may be present.

Concerning *natural immunity from the effects of poisons*, or *natural lack of susceptibility to poisons*, we know little at the present time; still, without doubt, many poisons are only poisonous to certain organisms, and it is probable that mankind is relatively insusceptible to many poisons that are deadly to certain animals. This is true, for example, with regard to the toxic proteids and the organic bases which are derived from bacteria and also from higher animals (serpents) and plants. If one takes into consideration that many animals are slightly or not at all susceptible to poisons which act powerfully upon the human body—that, for instance, the hedge-hog is not susceptible to the cantharidal poison and to the bite of poisonous snakes; that birds experience no bad effects from atropin and opium, nor goats from lead and nicotine; and, finally, that dogs, rats, and other animals used in experiments show a relatively greater resisting power to bacterial poisons and also to vegetable alkaloids than does the human being—it seems very probable that the converse may also be true. From this it would be proper to conclude that the natural insusceptibility of man to many of the infectious diseases of animals rests upon his powers to resist the toxalbumins and toxins which the bacteria belonging to these diseases produce.

The acquisition of relative or absolute immunity from poisoning by certain infecting germs and poisonous substances is generally produced by either a single infection or intoxication, or by repeated infections or intoxications, which leave behind such an effect upon the body that it is no longer susceptible to the corresponding micro-organisms or poisons—in other words, that it can no longer be made ill by these micro-organisms or poisons. Besides, it often happens that the fact of an individual's having passed through an attack of an infectious disease confers on him a relative or absolute insusceptibility to a disease which is closely related to it.

The great importance which natural predisposition and immunity possess with reference to the origin of infectious diseases is confirmed not only by the consideration of the spread of plagues among men and animals, but much more by numerous experimental researches. If a mixture of diverse bacteria is injected into an animal, only a part of them develop and produce tissue-changes; the others die. If the same mixture be injected into another animal of a different species, the bacteria which develop will be of different varieties from those which developed in the first instance. Further, a certain kind of Schizomycetes, inoculated into a certain species of mouse, produces certain death, but when the same kind is injected into another species of mouse it proves harmless. Mice are very susceptible to anthrax; rats are nearly immune. The poison of the so-called septicæmia of rabbits kills with absolute certainty rabbits and mice; guinea-pigs and rats are, on the contrary, immune, while sparrows and pigeons are susceptible to the poison. The spirilla of relapsing fever can be successfully inoculated only in apes. Gonorrhœa, syphilis, and leprosy cannot be successfully inoculated into any species of animals.

Different animals of the same species, but of different ages, show dissimilar behavior in this regard. Young dogs are easily infected by anthrax (Koch), while old ones are not.

Diverse experiments have shown that, by suitable action upon the tissues, an existing immunity from the effects of a certain infection can be rendered powerless.*

According to Roger,† the natural immunity of rabbits and pigeons in respect to anthrax can be overcome by injecting the non-pathogenic *Bacillus prodigiosus* at the same time that the anthrax is inoculated. The effective agent in this procedure, according to this author, is a decomposition product of the *prodigiosus* that is soluble in glycerin, and that produces a modifying action on the organism.

According to Gottstein,‡ guinea-pigs may be made susceptible to the subcutaneous injection of hen-cholera bacilli, in respect to which they have a natural immunity, by previously injecting subcutaneously substances which dissolve blood-corpuscles, as hydracetin or pyrogallol; and he is of the opinion that toxic substances which make men or animals susceptible to infections act chiefly through their power of dissolving the blood-corpuscles. According to Leo,§ white mice, which are immune in respect to glanders, may be made susceptible by mixing with their food a slight amount of phlorrizin, which produces a toxic diabetes.

According to Canalis and Morpurgo,‖ pigeons may be made susceptible to anthrax by hunger.

The *special diseases* to which the *new-born* frequently succumb (aside from those which begin in intra-uterine life) are dependent partly upon a pathological weakness of the entire organism (especially in those born prematurely), partly upon the particular surroundings in which they are placed. Asphyxia, which is of such frequent occurrence, may either originate from a weakness of the body or from pathological influences exerted during delivery. Infectious diseases may be acquired from infection through the cord, or through the accessible mucous membranes and the respiratory apparatus, during the passage through the parturient canal. Hæmorrhages are dependent partly upon traumatic influences during birth and partly upon circulatory disturbances and infections. Icterus in the new-born is sometimes the result of a change in the mode of nutrition (reabsorption of the bile out of the meconium); sometimes, however, it is the result of infection.

Children are, according to the observations of medical men, *more susceptible than grown people to many infections;* this is particularly true, for instance, with regard to whooping-cough, diphtheria, measles, and scarlet fever. In this connection it should be noted that the slight liability or the immunity of many grown-up people is due to the fact that they became immune through having had the disease during childhood. Further, it is to be remarked that children are more exposed to certain diseases—for instance, tuberculosis—than grown people.

In advancing years hæmorrhages, softening of the brain and heart, cancerous growths, and the formation of gall-stones are especially frequent. Arterial diseases, designated by the term arteriosclerosis, and also gout, are seen already in the later years of middle life. This *predisposition in old age to certain diseases* depends in part upon degenerative processes, associated with early-developed senility of the tissues; in part also upon the circumstance that certain effects which years bring with them gradually accumulate, so that finally the alterations which they produce become so prominent that they lead to disturbance of function, and ultimately to recognizable morbid conditions. In general it is to be observed that many pathological symptoms of old age are secondary diseases, which show themselves only after other tissue-changes have reached a certain degree. We may mention, for example, hæmorrhages of the aged, senile gangrene, and softening of the brain and heart, resulting from morbid processes in the arteries.

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* Sirotinin, "Die Uebertragung von Typhusbacillen auf Versuchsthiere," *Zeitschr. f. Hyg.*, i., 1886.

† "Contribution à l'étude expérimentale du charbon symptomatique," *Revue de méd.*, 1891.

‡ "Beiträge zur Lehre von der Septikämie," *Deutsche med. Wochenschr.*, 1890.

§ "Beiträge zur Immunitätslehre," *Zeitschr. f. Hyg.*, vii., 1890.

‖ "Ueber den Einfluss des Hungers auf die Empfänglichkeit für Infectionskrankheiten," *Fortschr. d. Med.*, viii.

The *predisposition of the sexes to special diseases* depends, in the first place, upon the peculiar construction and special functions of the genital organs; the conditions present in pregnancy and during the puerperium furnishing a specially favorable field for many diseases, as, for instance, infections from wounds. In general the diverse relations of the sexes to certain diseases are explained by the differences which exist between men and women as regards their respective modes of earning a livelihood, and, further, by the differences in the respective habits of the sexes.

Differences in the predispositions of different races are shown in such diseases as malaria and dysentery, to which negroes are in general less liable than Europeans. The Japanese are said to be more susceptible to beriberi than Europeans.

§ 29. **The acquiring of immunity with respect to a particular infectious disease** is a thing of frequent occurrence, and has been known by clinical observers to be a well-established fact for a long time past. This fact is established principally by the observation that the greater number of men are ill only once with any of the infections such as measles, smallpox, whooping-cough, scarlet fever, and diphtheria, and that after such an attack they remain exempt from the influence of this particular disease even when they expose themselves in all sorts of ways to the danger of contracting it. The knowledge of this fact is old, and early in the eighteenth century it gave rise, in the Orient, to attempts to produce in men immunity against the natural contagion of smallpox by the inoculation of material from the pustules of the disease. In the latter part of the last century, Jenner discovered that the disease called cowpox—i.e., a milder form of pox, which is either a special variety of disease closely allied to human smallpox, or a weaker form of the latter—also afforded protection against the true smallpox. As a result of this observation, since the beginning of the year 1796, at first by Jenner himself, and after him by the practitioners of all the civilized world, artificial inoculations of cowpox have been carried out upon millions of men, and with the result that through these inoculations a high degree of immunity from the true smallpox has been secured, so that at the present time, in countries where vaccination is practised universally, we no longer have the extraordinarily wide-spread epidemics of smallpox which were constantly occurring in former years, nor does the disease any longer assume the form of a dangerous epidemic.

The investigations with regard to the causes and origin of infectious diseases which have been undertaken during the last ten or fifteen years, and which have covered such a remarkably wide extent of pathological territory, have shown that **the acquisition of immunity against a certain infectious disease is acquired by a person's having once passed through an attack of that disease,** and that this mode of acquiring immunity holds good for a number of infectious diseases, especially those which run an acute course; furthermore, that this immunity is sometimes a transitory, sometimes an enduring peculiarity of the individ has had such an attack of the disease; and, finally, that when a pregnant woman acquires immunity she may transmit it to her child *in utero*. These observations have also shown that the **inoculation,** performed either once or repeatedly, **of attenuated pathogenic bacteria**—i.e., of bacteria which, on account of their decreased virulence, produce a disease that, in contrast to the natural infection with bacteria of full virulence, is merely a trifling affair, often confined to a circumscribed area—can also bestow, upon the individual so treated, immunity with regard to the corresponding disease. It has even been demonstrated that, for the production of insusceptibility to a certain disease, **it suffices to inject certain chemical substances produced by the bacteria of that disease.**

In explaining how immunity from an infectious disease is acquired through the fact of once having had the disease, or by inoculation, we can as yet give only hypotheses; but it is a matter beyond dispute that the last few years have brought great increase to our knowledge concerning the forces which effect this immunity, and we have now reached a point where we at least know in what direction further researches should be made.

After Pasteur had, in 1880, by experimentation proved that chickens could be made insusceptible to chicken-cholera by inoculation with attenuated chicken-cholera poison, and after it had been established by the repeated researches of various authors that similar results could be obtained with anthrax, symptomatic anthrax, and hog-cholera, they believed they could explain acquired immunity by saying that, through either the inoculation or the first overcoming of the particular infectious disease, the food-material in the body had been destroyed (Pasteur, Klebs), and consequently that the bacteria which entered the body later were unable to find food for themselves. This theory, termed the *exhaustion theory*, does not agree with the observed facts, and consequently at present it is generally no longer advocated. Metschnikoff's view that, in consequence of the preventive inoculations, the mesodermic cells become accustomed to the inroads made upon their substance by the previously undisturbed virulent bacteria, and that when the latter are again introduced they quickly take them up and destroy them, cannot in any wise be considered as an hypothesis possessing scientific foundations.

According to the facts which have been ascertained by investigations concerning the natural protective powers of the body against infections, and concerning the natural mode of recovery from such infections, as also by the experiments made with regard to protective inoculation and with regard to the artificial healing of infective diseases, it is very probable that *the acquired immunity is dependent upon the presence of certain chemical substances which are either poisonous to the particular variety of bacteria under consideration, or in some manner or other render harmless the poisonous products formed by these bacteria.* (This is known as the *poison theory.*) It remains an unsettled question, however, whether these substances are the product of the bacteria or of the body-cells; further, whether the abolition of the poisonous action of the bacterial toxalbumins and toxins results from their destructive decomposition, or from the formation of some harmless combination of these substances, or from an immunizing of the cells with respect to these particular poisons.

Some light is thrown upon this question by the past experiences in regard to the different ways in which it is possible to obtain, not only in experimental animals, but also to a certain extent in the human being, immunity as regards certain infectious diseases. Some further light is also obtained from experiments concerning the artificial healing of infections which have already become manifest. As heretofore stated, it is possible in animals to produce, in agreement with the results obtained by Jenner's cowpox inoculation, an immunity through the **inoculation of attenuated specific disease-germs.** This has been accomplished in anthrax, for instance, in symptomatic anthrax, in chicken-cholera, in diphtheria, and in swine-plague. According to the researches of Pasteur, an immunity against hydrophobia can be produced in man by the injection of the poison in an attenuated form, even after infection by the bite of a rabid animal has taken place.

The weakening of the virulence of bacteria is produced either by the action of high temperatures or by that of chemical agents, or by the air only; further, it is also produced by the inoculation of certain animals with the bacteria, and by long-continued cultivation of them on artificial media. Inoculation is generally carried out by injecting first markedly attenuated, then less attenuated, and finally fully virulent bacteria, along with their products, beneath the skin.

According to the investigations of Salmon, Smith, Pasteur, Foà, Bonome, Perdrix, Charrin, Roux, Chamberland, Singer, C. Fränkel, Klemperer, and others, immunity may be produced by the injection of **sterilized cultures** in which the contained bacteria are dead. The diseases which may be warded off in this manner are the following: American hog-cholera, symptomatic anthrax in cattle, diphtheria, the infectious disease produced in rabbits by the injection of the *Bacillus pyocyaneus*, and the infection produced in guinea-pigs experimentally by cholera-spirilla. Probably the immunizing substances are contained in the cell-substance of the bacteria (Brieger, Kitasato, Wassermann).

A third form of artificial immunizing, which Raynaud tried as early as in 1877, but which was first securely established by Behring in 1890, can be produced by the injection, into an experimental animal or even into man, of **blood-serum taken from animals which were previously susceptible, but which had been artificially rendered immune by means of inoculations.** The most extensive and at the same time the most successful experiments thus far made have related to *tetanus* (Kitasato, Tizzoni, Buchner) and *diphtheria* (Behring)—that is, to diseases in which the most striking feature is an intoxication by means of toxalbumins. Besides these, reports have been published of successful experiments with the blood-serum of immunized animals in croupous pneumonia (Emmerich, Foà, G. and F. Klemperer), cholera infection of guinea-pigs (G. Klemperer, Issaeff), swine-plague (Emmerich), and anthrax (Ogata).

As the result of his researches, Behring concludes that, "if an individual has been artificially rendered insusceptible to a certain disease, his blood, as well as the serum which can be separated from it, has thereby acquired the power to communicate the condition of immunity to an individual of the same species who is susceptible to the same infectious disease, provided it be introduced into his system *in a sufficient quantity*."

According to the observations which have thus far been published, the specific protection which the blood-serum affords can be secured not only by injections which are made before infection takes place, but also by injections which are made after infection has already occurred; thus justifying us in speaking of the serum not only as a *protective*, but also as a *healing serum*. Further experience has also shown that both for the prevention and for the cure of a particular infection a certain amount of serum is necessary, the precise amount depending, on the one hand, upon the severity of the infection, and, on the other, upon the activity of the serum itself, which increases with the completeness of the immunizing of the original susceptible individual who furnished the serum. If the injection is not made until after the infection has occurred, the amount of serum injected must be greater the longer the time which has elapsed since the infection took place.

How the serum produces immunity cannot yet be accurately determined; the active protective agent, however, is a definite substance which the serum contains, and which may properly be called an *antipoison* or *antitoxin*. The chemical nature of this substance is not known precisely, but it is probable that it belongs to the albuminoid bodies. Its mode of action in tetanus and diphtheria is manifested in one of two ways: it either destroys the specific bacterial poisons (Behring), or it protects the tissues against the action of the bacteria (Buchner, Tizzoni, and others) —that is, renders them insensitive to their action. It is therefore more proper to term the so-called healing serum *immunizing serum*, and that, too, even when it is used for the first time after the infection has taken place, since also in such cases the action consists in immunizing those tissues which have not yet become infected. In certain cases the action of the healing serum may lie in the destruction of the bacteria, as, for instance, in the case of the infection produced by the pneumococcus (Emmerich).

The origin of the immunizing substance in the blood is still an unsolved problem. One may suppose that it is the product of an especial activity of the cells of the infected organism; yet it is very difficult to reconcile this theory with the fact that these substances which produce immunity protect only against the particular form of disease in whose course they have originated; the tetanus antitoxin, for instance, being active only against tetanus, and the diphtheria antitoxin only against diphtheria. It is better to explain the phenomena by the supposition that the antitoxins are substances which are produced by the bacteria themselves, or that the bacteria at least provide the material for the making of the antibody. Buchner is of the opinion that the antitoxins are specific bacterial cell-substances. On this theory the immunization by means of healing serum would be effected in somewhat the same manner as it is by the injection of sterilized or attenuated bacterial cultures. The distinguishing characteristics of the different modes of immunizing may then be stated as follows: in the injection of attenuated cultures (vaccine) the production of the immunizing substance occurs partly in the cultures, partly in the person inoculated; in the injection of sterilized cultures it takes place only in the cultures; and, finally, in injections of the so-called healing serum it takes place in the animal from which the serum is obtained.

For the foundation researches in regard to attenuated inoculation cultures grown in culture-media outside of the body we must thank Pasteur, who, in the year 1880, discovered the fact that by the inoculation of cultures of chicken-cholera bacilli, which had become attenuated by remaining for a long time in the air, chickens could be made insusceptible to this disease.

Since that time numerous experiments have been carried on with other forms of bacteria—for example, with attenuated anthrax-bacilli, with symptomatic anthrax-bacilli, and also with the poison of rabies—for the purpose of ascertaining whether immunity in respect to other infections might be obtained. The best results have been obtained from inoculations of cattle against symptomatic anthrax. The results obtained by the inoculation of anthrax have been less successful, a portion of the animals dying from the inoculation, while in others no absolute immunity was obtained against a new anthrax infection.

Sheep and cattle may be made insusceptible to anthrax, and most easily in the following manner (Koch): they are first inoculated with attenuated bacilli which will kill mice, but not guinea-pigs; then with bacilli which will kill guinea-pigs, but not strong rabbits.

As vaccine against symptomatic anthrax, bacteria should be employed which have been attenuated by heat or by chemical agents, such as sublimate solutions, thymol, eucalyptol, and nitrate of silver; and by inoculations of this character cattle may be rendered immune. At the present time heat is most commonly used in preparing the vaccine (Hess, Kitt). A piece of infected muscle is taken from an animal that has died of symptomatic anthrax, and chopped into small bits; then it is mixed with one half its weight of water, and squeezed through a linen cloth. Finally, the fluid is again filtered through a moistened piece of linen. This virulent mass is first spread upon glass plates or flat dishes, and then transferred to a dry chamber where the temperature is kept at from 32° to 35° C. (89.6° to 95° F.). When thoroughly dried the virus may be scraped off and removed in the form of a powder. If one wishes to produce material for inoculation from this virulent virus, it should be triturated with double its weight of water, and this fluid is then to be steamed in a thermostat. By raising the temperature to 100° C. (212° F.) during six hours, one gets a weak immunizing material; by the action of a temperature of 85° C. (185° F.) for six hours, a more active preparation is produced. For immunizing an ox or a cow, about 0.5 gramme of a thin watery solution of the weak vaccine should be injected, preferably into the subcutaneous cellular tissue near the animal's tail; and, after the lapse of from eight to twelve days, the stronger solution should be injected in a similar manner.

Hogs, according to Pasteur, may be made insusceptible to inoculation with virulent hog-cholera bacilli by the employment, as vaccine material, of bacilli which have become attenuated through a series of inoculations of rabbits. According to Emmerich, rabbits may be made insusceptible to swine-erysipelas bacilli by the injection, into the veins of the ear, of small amounts of virulent bacilli-cultures diluted fifty-fold with water.

For animals susceptible to diphtheria, immunity may be procured, according to Behring, by the injection, into their abdominal cavity, in small amounts (2 cubic centimetres), of cultures of diphtheria-bacilli which have been attenuated by exposing them for sixteen hours to the action of iodine trichloride (1 to 500); and then, after the lapse of three weeks, by the employment of another injection containing a diphtheria-culture (0.2 cubic centimetre) which has been permitted to grow for four days in bouillon to which iodine trichloride (1 to 5500) has been added.

According to Emmerich, rabbits may be made completely insusceptible to pneumococci by injections, first, of 0.3 cubic centimetre of a strongly virulent bouillon-culture diluted in the proportion of 1 to 5000, and afterward of bouillon-cultures of full virulence.

Protective inoculations against rabies are resorted to only after the individual has actually been bitten by a rabid animal, and the practice is employed chiefly in France (at the Pasteur Institute), in Russia, and in Italy. For inoculation purposes it is customary to employ the spinal cord (desiccated in dry air at a temperature varying from 23° to 25° C.—73.4° to 77° F.) of rabbits in whom the disease has been created artificially. By means of this drying process, continued for a period of about fifteen days, the cord gradually loses its poisonous character. According to Protopopoff, it is not so much the drying as it is the heat which diminishes the virulence of the poison. From this piece of spinal cord, possessing diminished poisonous properties, small bits are taken and rubbed up in sterilized chicken-broth. Some of this mixture is then injected beneath the skin of the person who has been bitten; only a very weak
being employed at first, but afterward the strength being gradua
It is Pasteur's opinion that the spinal cord, under the condit

considering, contains partly microbes and partly a specific poison which they have produced; and that this poison, if it become distributed throughout the body more rapidly than are the microbes, will confer on the organism immunity from the effects of a subsequent invasion of these microbes, and especially will protect the nervous system. It is therefore necessary, if we wish to secure the desired degree of immunity, to introduce into the system as large quantities as possible of the chemical poison. The published reports of the institutes in which the Pasteur protective inoculations against rabies are made warrant the conclusion that these inoculations do actually prove effective in warding off an outbreak of rabies.

According to the observations of Chauveau and others, it is possible, in making protective inoculations, to adopt the plan of injecting virulent bacteria in very small quantities, or in such a manner that they shall not be injurious to life. In symptomatic anthrax, for example, this result may be obtained, in oxen or cows, by injecting very small quantities of the fluid into the extremity of the animal's tail; these injections not causing a fatal illness, but merely some local disturbance.

If we inject into the tip of the ear of a rabbit the bacilli of mouse-septicæmia, from a pure culture which would, under ordinary inoculation, kill rabbits in from forty to seventy-two hours, there is produced a progressive inflammation of the skin which does not kill the animal, but which, in from three to four weeks, produces an immunity from the effects of future inoculations.

According to the researches of Schuetz, cattle may be rendered insusceptible to contagious pleuropneumonia by injections of the tissue-juices obtained from the lung of an animal suffering from the disease, provided only a short time shall have elapsed since it died from the disease or was killed, and provided the injections be made into the tail. There is produced by this means a localized inflammation, or one, at least, that is confined to the tail; and after it has quieted down, the animal will be found to be insusceptible both to the natural infection and to an infection of artificial origin.

According to the researches of Ehrlich, mice may be made immune against *ricine*, to which they are most susceptible, by mixing very small doses of it with their food, and then afterward injecting additional small doses beneath the skin. The appearance of the immunity first shows itself six days after the first dose, so that upon this day the animal can withstand a dose thirteen times as great as at the beginning. By means of continued systematic inoculations the animal is rendered insusceptible to a dose eight-hundred-fold stronger. The immunity is produced by an antitoxic substance, antiricine, which suspends the action of the poison.

In regard to the *cure of diseases by the use of blood-serum from animals that have been rendered artificially immune*, we possess observations, valuable for man, on tetanus and diphtheria. The most exhaustive researches have been made with regard to tetanus (by Kitasato, Behring, Tizzoni, Cattani, and Buchner), and, so far as animals are concerned, the results are certain. When used in man, the injections of the curative serum of tetanus have not as yet given entirely satisfactory results; nevertheless the observations of Tizzoni, Gagliardi, Schwarz, von Ziemssen, and others seem to show that it exerts a favorable—i.e., a curative—effect. Tizzoni claims that only 20 per cent. of the tetanus cases which have been inoculated die, while ordinarily 88 per cent. of those ill of this disease perish. The difficulty in using the antitoxin in the treatment of tetanus in the human being lies in the fact that the persons attacked come under observation relatively late after the infection has taken place, so that, in order to procure recovery, extraordinarily large doses of the antitoxin are necessary. According to Behring, the curative serum derived from horses is the best, and can be made unalterable by the addition of 0.5 per cent. of carbolic acid. According to Buchner, the tetanus toxin may be precipitated by sodium ammonio-sulphate, and when dried forms a powder of great durability.

Behring has been most prominent in the study of the *curative serum of diphtheria*, and obtains it from immunized sheep. Experiments conducted on animals give favorable results. Concerning the availability of the serum in the treatment of human beings who have been taken ill with diphtheria, we cannot as yet give a definite judgment; still in the cases treated by Behring the mortality was less than it usually is.

According to Emmerich, the pneumococcus infection in rabbits and white mice may be cured by the injection of blood-serum from animals which have been rendered completely immune.

Individuals who possess a natural immunity against a certain disease have no immunizing substance in their blood-serum. This is first produced by artificial immunization. The value of the immunizing blood-serum is so much the higher the greater the difference which exists between the original predisposition and the immunity derived from inoculation. According to the researches of Ehrlich, the immunizing substances may be carried over into the milk, and the nursling may thus become immunized. The immunity produced by the curative serum is, as it appears (Ehrlich), of short duration, while that produced by the fact of having passed through an attack of an infectious disease in most cases lasts for a much longer time. Recovery from an infectious disease does not always produce immunity against the same disease, at least not in the sense that the individual who has thus recovered can remain for any great length of time immune. Individuals who have been ill from rheumatic arthritis, from pneumonia, or from erysipelas, often have the disease again; consequently the predisposition to these diseases certainly does not become permanently annulled. In fact, it sometimes appears as if the first illness predisposes one to subsequent attacks of the same sort. The repeated occurrence of attacks of the same infectious disease may be explained more correctly, as it seems to me, in one of two ways: either that from the very first there existed a predisposition which could not be overcome entirely by the act of passing through an attack of the infection; or that some of the bacteria belonging to the particular disease had continued to remain in the body.

As the result of a communication made by R. Koch in 1890, during the years 1890, 1891, and 1892, both in Germany and in other countries, an extraordinarily large number of attempts to cure tuberculosis were made with an extract derived from cultures of tubercle-bacilli. These attempts were made in cases of tuberculosis both of men and of animals, and it was believed that the substance termed *tuberculin*, which contains bacterial proteins as the active healing principle derived from the cultures, exerted a healing influence upon the tuberculous process. The enthusiasm with which the hoped-for remedy was received soon gave way to bitter disappointment. In certain stages of the disease the tuberculin induced inflammation in the tissues which had been altered by tuberculosis, and this inflammation and the accompanying proliferation of the tissues may, under certain conditions, exert *locally* a beneficial effect on the progress of the disease. Tuberculin, however, produces no immunizing effect upon the tissues, does not kill the tubercle-bacilli, does not even act on all tuberculous foci, and the inflammation produced by it may have a deleterious effect, and may basten the spread of the disease through the body.*

According to the researches of Stern, the blood of human beings possesses a protective power against the typhoid infection produced experimentally, and this power is especially marked in the blood of convalescents from the disease, and less so in that of healthy men. According to this author, the protection is secured by reason of the fact that the serum acts on the organism to be protected, and enables it to render the infecting bacteria harmless.

VII. The Intrinsic Causes of Disease and the Inheritance of Pathological Conditions.

§ 30. Among the **intrinsic causes of disease** must be mentioned, first, all those peculiarities which have their foundation in the organization of the individual and owe their origin to some congenital local predisposition, and which, furthermore, superinduce diseases independently of outside influences—i.e., without the aid of any other influences except such as our relations to the outside (more or less harmful) world necessarily bring with them. When morbid processes arise in this manner we speak of the special disease or of the special malformation thus arising as of spontaneous origin. In a broader sense we may also reckon among the intrinsic causes of disease the individual peculiarities which have been described in the last chapter (VI.), and to which the names predisposition and idiosyncrasy have been applied; but we are justified in doing this only in so far as the diseases in question clearly owe their immediate development not merely to the action of some outside injurious influence, but also at the same time to the existence of a predisposition or of an idiosyncrasy.

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* A summary of the literature on the action of tuberculin may be found in the *Jahresbericht* of Baumgarten, in the *Centralblatt für Bakteriologie*, and in the *Centralblatt für allgemeine Pathologie*, of the years 1891 and 1892.

Among the morbid conditions which arise from strictly internal causes—i.e., without the aid of specific external influences—and which either appear of themselves or are brought to development by some external influence, it is possible to distinguish different groups, namely, one in which the body as a whole—the constitution—is involved; another, in which only a portion of the body, or a system, shows itself to be functionally deranged or perhaps even pathologically altered in its structure; and, finally, a third, in which either a single organ or even, perhaps, only a part of an organ manifests these functional or structural alterations. At the same time it should be stated that no sharp dividing-line exists between these groups, for local pathological alterations may be associated with constitutional conditions. Then, again, it should be remembered that very frequently it is not only difficult, but at times impossible, to determine what part internal conditions and what part external exciting causes are playing in the production of a pathological condition, since we cannot measure the force of the external influence which has called into activity the pathological processes.

Among the **constitutional diseases arising from internal causes** are to be mentioned, in the first place, the *development of dwarfs* and the *development of giants*—i.e., disturbances of growth, of which the first is marked by an abnormal deficiency in the growth of all the parts of the body, of the skeleton as well as of the soft parts; while the second is characterized by a growth exceeding that of the ordinary individual. It cannot be doubted that both the dwarf and the giant growths are dependent on a congenital tendency; but the same effects can be produced, at least so far as the inhibition of growth is concerned, by harmful influences during the period of gestation and during later development, so that it cannot be always told with certainty whether an abnormal bodily growth is dependent upon a congenital tendency or upon pathological influences which have occurred during the period of growth (see § 22)—as, for instance, disturbances of growth due to disease or to the loss of the thyroid gland.

The same difficulties are encountered when we attempt to explain the cases in which the body has perhaps attained a normal development of height, but manifests a general feebleness—a constitution which has no power to withstand a great variety of external influences; for this condition may arise from an inherited weakly and defective body, or from harmful influences which have attacked it during intra- and extra-uterine development; and, again, a congenitally weak body and outside weakening influences may both have acted upon the growth of the individual in a similar manner.

Another constitutional peculiarity which may owe its origin to an inherited special predisposition is **corpulence** (*obesitas, adipositas, lipomatosis universalis*)—a condition in which fat is either deposited in excessive quantity only in tissues which normally should possess fat, or else is deposited also in regions which normally contain no fat, as, for instance, under the endocardium or between the muscles. In the ultimate analysis of this condition it must be recognized that this heaping up of fat in the body is always dependent upon a disproportion between fat-production (that is, the supply of fat to the parts) and fat-consumption; this disproportion showing itself at one time in the form of greatly increased fat-production, at another in that of an abnormal decrease in fat-consumption. As daily observation teaches, the energy with which metabolism goes on in the body is very different in different individuals, and changes also at different periods of life, so that the same amount of food tends at one time to fatten, while at another time it shows no such tendency.

In the pathological constitution termed obesity, which sometimes depends on a congenital predisposition, the energy of the protoplasmic forces of destructive metamorphosis is weakened, so that an abnormal amount of fat collects even when a moderate or perhaps only a slight amount of nutritive material is supplied to the tissues.

Gout, like obesity, is also a constitutional disease, which for the most part is dependent upon a constitutional inherited tendency, and consequently depends chiefly on internal causes. Exactly what is the essence of the disease we are unable as yet to state. One of its characteristic features is that a patient with this disease is subject to attacks in which deposits of uric acid are made in the tissues. According to Garrod and Ebstein, acute attacks of gout are dependent upon a stagnation of uric acid, which either has its origin in the kidney or in local conditions. Pfeiffer, on the other hand, is of the opinion that the essential feature of a gouty predisposition consists in the fact that the uric acid is produced in a form which is soluble only with difficulty. According to von Noorden, the production and deposit of uric acid are only secondary phenomena, which are induced by the presence of a particular ferment, which acts only locally and consequently is not dependent upon the amount and the behavior of the uric acid which is formed in another part of the body.

Pathological changes which arise in single systems and organs from internal causes may manifest themselves in all the tissues of the body, and they involve at one time an entire system or organ, at another only a part of one.

In the *skeleton*, in the first place, we may mention the following changes as illustrating what we have just stated: abnormal developments, as regards size, of single parts—e.g., abnormal smallness of the extremities (micromelia), or of the head also (microcephalus), in contrast with the trunk; or the abnormal size of one bone or of a group of bones (macrocephalus; the abnormal increase in the length of the fingers; great growth of one finger, or of an entire foot, or of an extremity; the formation of ribs in the neck, etc.). Occasionally supernumerary bones are developed—for instance, bones in the wrist or phalanges, thus leading to the formation of supernumerary fingers. There can also be developed atypical formations, such as bony growths (exostoses, hyperostoses), which may extend over a larger or a smaller portion of the skeleton, and may originate either spontaneously or as a result of some traumatism.

In the *muscular system* are to be noted the production of pathological bony formations, which occur either singly or in multiple form (myositis ossificans), and occasionally, in the period of childhood, give rise to a progressive stiffening of the muscular apparatus, by the transformation of the muscles into osseous scales or plates.

In the *vascular system* the lesions which are found consist in part of gross anatomical alterations—such as an abnormal division of the arteries, or some pathological development of the heart—and in part of more delicate alterations, which reveal their existence only through some abnormal action on the part of the circulatory apparatus or through a tendency manifested by the patient to hæmorrhages (hæmophilia) which take place spontaneously—i.e., without our being able to show that an injurious influence has been exerted upon the heart and blood-vessels.

Some of the *primary disturbances which the development of the nervous system experiences* manifest themselves only by some pathological disturbance of function, or by a special predisposition to various forms of illness; while others are distinguished by gross—i.e., by perceptible—anatomical changes, such as abnormal smallness of the cerebrum (micrencephalon) or of the spinal cord (micromyelia), defective or absent development of particular parts (compare the section on Malformations), misplacement of the gray substance (heterotopia of the gray substance), the abnormal formation of cavities (syringomyelia), abnormal formations of the neuroglia, etc. These disturbances may involve the functions of the organs of sensation and of the motor areas, as well as, and to an even greater extent, the psychical processes; and the pathological conditions termed idiocy, epilepsy, periodical and circular insanity, hysteria, and neurasthenia, as well as paralysis, mania, melancholia, and dementia, may have their origin in a congenital predisposition. Lately some persons have attempted to refer the tendency to crime to a congenital predisposition; and Lombroso in particular has sought to prove that the person who depends for his support upon crime and lives only for criminal purposes —the *homo delinquens*—is a congenital criminal—i.e., he is a man who suffers from bodily and mental abnormalities; possesses other physical and psychical characteristics than those which belong to the normal man, or even to one who is simply mentally diseased; in a word, he must be looked upon as presenting the symptoms of a special form of degeneration that tends in a well-defined direction. According to Lombroso, a subnormal development of the anterior half of the cranium, together with a corresponding lack of development of the anterior portion of the cerebrum, when associated with an increased development of the posterior portion of the brain, necessarily produces a feebler development of the intelligence and of the moral sense, and favors a strongly developed instinct-life. Benedikt even went so far as to maintain that we can distinguish in criminals a peculiar configuration of the cerebral convolutions, which are similar in type, as he claims, to those of animals of prey.

The views of Lombroso and Benedikt have met with opposition from various quarters, and have been attacked as incorrect; and there can be no doubt that there does not exist a species of human beings who are characterized by definite anatomical peculiarities by means of which one can say that they belong to the class termed *homo delinquens* in contradistinction to that of the *homo sapiens;* for all the bodily peculiarities which have been mentioned as characteristic of the criminal type—as, for instance, the beast-of-prey type of cerebral convolutions, the feebly developed frontal brain, the receding forehead, massiveness of the lower jaw, prognathia, asymmetry of the skull, marked prominence of the arcus superficialis and of the arcus frontalis, pathological conformations of the skull, etc.—are indeed frequent in criminals, but they are also far from infrequent in perfectly normal men.

It is, however, not to be doubted that the tendency to criminality is very often dependent on a congenital predisposition, which is found in some special organization of the central nervous system; that, in this regard, the criminal has some resemblance to the insane person; and that, also, mental diseases—for instance, epilepsy and hysteria—are often observed in criminals. The pathological cerebral functions in persons who are pathologically predisposed to this class of diseases may develop primarily—i.e., without external agencies having any influence on the disturbance; and under these circumstances the person concerned, even during the time of development and growth, or sometimes also later, manifests pathological changes in the functions of his cerebrum without having received any external injury that might explain such changes. In other cases, on the other hand, external influences—such as mental work, sorrow, care, psychical irritation, disease, etc.—are the causes which give rise to the particular illness—i.e., to the outbreak of pathological brain or spinal functions. In these cases the inherited predisposition consists merely in an abnormal weakness, a tendency to disease of the central nervous system, which expresses itself in the circumstance that transitory influences which would not act noticeably on a normal person are sufficient, in the case in question, to produce the morbid phenomena. Inasmuch as many influences—such as diseases, infections, psychical irritations—are adequate, under certain conditions, to produce mental disease in individuals whom one must look upon as normal, so it is clear that, in many instances, it is difficult, if not impossible, to distinguish what part the internal causes—the inherited predisposition—and what part the external causes have had in producing disease of the central nervous system.

As regards the *peripheral nerves*, it is especially their connective-tissue elements which often take on a pathological activity of growth under the influence of internal causes; and this activity manifests itself partly in the form of diffuse thickenings (fibromatosis of the nerves), partly in that of nodular thickenings (fibromata of the nerves), which either develop along the course of those nerves which are large enough to be dissected with the scalpel, or are scattered over the filaments of the finer nerves, often being present in large numbers throughout the areas of distribution of entire nerves, or even involving the entire territory supplied by the peripheral nerves, the skin being the part most often affected (multiple fibromata of the skin). In certain cases the fibromatosis of the nerves is associated with an increase in the number of nerve-fibres; and as a result of this change there will be found in a given territory of nerve-supply abnormally numerous bands of nerve-fibres, thickened by a pathological increase of the endoneurium, mostly thrown into serpentine or twisted shapes, or interwoven (cirsoid neuroma, plexiform neuroma).

Among the *pathological conditions of the visual apparatus* which arise from internal causes we should mention particularly dyschromatopsia and achromatopsia, the congenital partial or total color-blindness, both of which conditions are frequently spoken of as daltonism, and are characterized by a want of perception for a portion of the colors (most frequently red and green), or even for all the colors. And, further, in this same category belongs the typical pigment-degeneration of the retina, in which a peculiar spotted-black pigmentation of the retina is seen, while simultaneously the acuteness of central vision and the perception of light are diminished and the visual field is narrowed. Finally, there should be added to this list certain forms of myopia, as well as albinism (the absence of pigment in the choroid), the latter of which conditions also involves some of the appendages of the skin.

The only affection of the *organ of hearing* which, at least in part, can be considered as a primary developmental disturbance is deaf-mutism. Then, in the next place, we may also place in this category the various malformations of the external ear.

In the *skin* and *subcutaneous connective tissue* new growths develop, which are the result of congenital predisposition. These growths are formed sometimes almost entirely of connective tissue, sometimes of epithelial tissues; they also often involve particular portions of the skin, as the cutaneous nerves, the blood-vessels, the lymphatics, or the adipose tissue. When they take on the form of extensive thickenings of the skin and the subcutaneous cellular tissues, they constitute the foundation of the conditions termed fibromatous, neuromatous, hæmangiomatous, lymphangiomatous, and lipomatous elephantiasis. When they occur as circumscribed formations, they are known as birth-marks, soft moles, lentigo, freckles, and also as tumors of the lymph- and blood-vessels. Epithelial hypertrophy produces those changes which are called fish-scale disease or ichthyosis, ichthyotic warts, and cutaneous horns.

In addition to the pathological conditions which have been enumerated there are many *malformations of the body* (compare the section on Malformations), *or also of the internal organs*, which must be considered as of primary origin—i.e., which are not produced by the action of external influences on the already developing fœtus. Finally, many forms of *tumors* (see the section relating to Tumors) belong in this class, especially those which are found to be already well developed at the time of birth, or which undergo development during childhood.

§ 31. Two explanations may be given of the **mode of origin of those diseases which we attribute to internal agencies**—diseases, therefore, in which external influences are either entirely absent during both intra- and extra-uterine life, or simply possess the significance of being a source of irritation sufficiently active to cause the development of a disease germ already present in the body. These two explanations are the following: *either the pathological peculiarities of the particular individual are inherited from the ancestors, or they are developed from the seed—i.e., from the sexual nuclei that have copulated, or from the segmentation nucleus derived from such a combination.*

The **inheritance of pathological peculiarities** is a fact which we learn, in the first place, from clinical observations; for many of the instances cited in § 30 of diseases which result from internal causes are also illustrations of inherited tendencies within the family. In a certain number these peculiarities are transmitted from parent to child, while in other instances the hereditary factor is shown by the fact that the grandchild manifests the peculiarities of the grandparents, the parents themselves remaining exempt; sometimes, again, it is shown by the fact that scattered members of the family (the collateral branches being included) manifest the pathological peculiarities which are under discussion. Dwarfishness and abnormal largeness of the body are peculiarities which frequently enough characterize certain families. Six fingers, harelip, right-sided position of the heart, birth-marks, multiple bony excrescences on the skeleton, fibromatous nerves, and multiple nerve-fibromata may appear in many generations of one family.

Congenital hæmophilia is also an inheritable pathological peculiarity, which in the descent is transmitted generally by the offspring to the male grandchild, whereby the daughters aid in the transmission, without themselves suffering from hæmophilia. There may be, however, a direct transmission of the hæmophilia to the children. Partial and total color-blindness is also sometimes an inherited family disease which attacks particularly the male members, and, like hæmophilia, is transmitted through the female line, which does not suffer, to the male descendants. Typical pigmentation of the retina is inheritable, as are also near-sightedness, deaf-mutism, and certain forms of progressive muscular atrophy and polyuria (Weyl).

Gairdner and Garrod state that in about 90 per cent. of all cases suffering from gout the disease also existed in their forefathers.

Of the pathological conditions of the nervous system, many are transmissible; to these belong especially periodical and circular insanity, epilepsy, hysteria, and congenital madness (*originäre Verrücktheit*), and, to a somewhat less extent, melancholia, mania, frenzy, and alcoholism; while the progressive paralyses, the deliriums, and the conditions of mental exhaustion are but slightly influenced by heredity (Kraepelin). Hagen estimated the number of hereditary insane at 28.9 per cent., Leidesdorf at 25 per cent., Tigges at over 40 per cent. of all cases, and Forel holds that from 69 to 85 per cent. may be accounted for by heredity.

In the most severe forms of hereditary degeneration the pathological conditions themselves are inherited; but more frequently the hereditary influence only produces a predisposition to disease, and the actual morbid condition first shows itself only after the central nervous system has been acted upon by some external injurious influence. The form of the disease may remain the same in the descendants as in the ancestors (*identical heredity*). More frequently a change takes place in the form of the disease (*transformational heredity*), not infrequently in the sense that the severity of the disease increases from generation to generation, a condition which is termed *degenerative heredity*.

According to Morel, there may appear, for instance, in the first generation, nervous temperament, moral depravity, excesses; in the second, a tendency to apoplexy, severe neuroses, and alcoholism; in the third generation, psychical changes, suicide, intellectual incapacity; finally, in the fourth generation, congenital imbecility, malformations, arrests of development.

As already stated in § 28, the special predispositions to this or that disease which individual families or sometimes entire races show are hereditary peculiarities. Thus, for example, it cannot be doubted that certain families have a stronger predisposition to certain infections (tuberculosis) than others. But, on the other hand, it often happens that insusceptibility to certain injurious influences is a valuable attribute of a family.

There is nothing at all strange in the fact that there are **inheritable diseases,** since it is a well-known fact that in a family not only the peculiarities of race, but also those of that particular family, may be inherited, and that the qualities characteristic of one or the other or of both parents often enough recur in the children. In order that hereditary transmission may take place, it is simply necessary that the peculiar quality under consideration should represent not merely a somatic change accidentally acquired in the course of the life of an ancestor, but rather an individual peculiarity of this ancestor which he in turn had inherited from his forefathers. Diseases which, in a normal individual, originate only when he is subjected to external harmful influences are never in the true sense inherited (see § 33); this expression can be employed only in regard to those *pathological conditions which already existed in the germ.* If, for example, a disease—such as a mental disease or near-sightedness—is the product of a special inherited predisposition plus the effect of harmful influences which have acted upon the body during life, only that part can be transmitted which was received by inheritance, but not that which was derived from external influences—i.e., the part which was acquired.

In *direct inheritance*—i.e., in that form of inheritance in which parental peculiarities are transmitted to the child—the transmission of both normal and pathological qualities can only take place when both sexual elements, in the condition in which they are at the moment of their union, contain, in a potential form, the characteristics of both parents, in so far as these characteristics are of a transmissible nature; and consequently the product of their union—the segmentation-cell—must then contain within itself both the paternal and the maternal qualities. Since the sexual cells do not represent a product of the body which is formed only after a certain stage in the course of life is reached, but should rather be looked upon as independent formations which, located in special organs, separate themselves at an early period from the rest of the body (that is, from the somatic cells) and then—continuing to derive their protection and nourishment from the body to which they belong—lead an independent life, there remains but one way in which we can explain the phenomenon of inheritance: we must assume that the separate sexual cells contain, from the time of their origin onward, essentially the same characteristics (in a potential form, of course) as belong to the body in which they dwell; in other words, that the sexual cells, as well as the body itself, have inherited in general the same qualities from the ancestors. Since in the act of fructification only the nuclei of the sexual cells—i.e., only parts of them—come to copulation, we are compelled further to assume that the bearers of these qualities are only the nuclei, and that the peculiarities belonging to the individual who grows out of this combination of the sexual nuclei reside in and are bound up with the organization of the nuclei.

If there appear in the descendants normal or pathological characteristics which are found collaterally (in an uncle, a great-aunt, or a cousin), but not in the parents, this is spoken of as *collateral hereditary transmission;* in this case the only supposition that will explain it is that the sexual nuclei, in their origin, received characteristics which the bodies of the parents did not contain; or, at all events, we may assume that these characteristics did not undergo development and become manifest in these bodies, whereas in some of the relatives they did thus become manifest.

If there appear in an individual normal or pathological characteristics which were wanting in his parents, but were present in the grandparents or great-grandparents, this is spoken of as an *atavistic hereditary transmission;* and the appropriate explanation of this is to be found in the fact that the peculiarity of the grandparents or great-grandparents was transmitted to the sexual nuclei of the son—i.e., of the son and grandson—but did not develop in the body of the first, while this latent quality manifested itself again in the grandson and in the great-grandson.

The attempt has been made to give to the atavistic mode of transmission—which is of frequent occurrence and is confined to the nearest generations of the ancestors—a wider significance in pathology. Thus it has been proposed to explain many newly arising pathological manifestations, which seemed to resemble certain somatic peculiarities possessed by remote animal species in the ancestry of man, as a reversion to the type of those ancestors. Thus, for instance, microcephalia and micrencephalia have been explained as a reversion to the ape type, and Lombroso is also inclined to look on his *homo delinquens* as an atavistic appearance. Nevertheless there is no doubt but that they have gone too far in this respect, and have characterized as atavistic formations various acquired pathological formations and fresh variations of germs (compare § 32). Aside from the question of a reversion to the type of the nearest generations of ancestors, atavism plays only a minor part in pathology, and it can really only be employed in the explanation of pathological formations when their tissues show a certain fluctuating behavior, characterized by the fact that frequently formations arise which in phylogeny or ontogeny represent the primary stages of the then normal conditions. In this category belong, for instance, the occurrence of certain forms of the ear or of supernumerary ribs, the increase in number of the mammary glands and nipples, the development of certain muscles belonging to the Mammifera which come nearest to man in the scale of relationship.

It is accepted by many authors that *in isolated cases acquired diseases may, under certain circumstances, be transmitted to the descendants,* and some even go so far as to say that the possibility of hereditary transmission may be conceded to a deformity sustained through injury; indeed, they consider that this has actually been proved for some instances. In support of their opinion, they believe that they are warranted in pointing to the hereditary transmissibility of birthmarks, malformations of the fingers, myopia, mental diseases, predisposition to tuberculosis, and other conditions, in regard to which they assume that these conditions in the first instance only showed themselves as acquired maladies, and that they were then transmitted to the descendants. Further, they believe that they can point to observations on animals—full accounts of many such observations are on record—as evidence that injuries give rise to deformities which later on are bequeathed to their offspring.

An unprejudiced examination, however, of the collected material which is brought forward in support of this opinion shows that *observations which establish the existence of such a thing as the hereditary transmission of acquired pathological characteristics in an individual do not exist;* that in the observations in question the defectiveness of the proof consists at one time in an error of observation, at another in a false inference from a correctly made observation. Take, for instance, the fact that in a child a birth-mark appears in a region of the skin exactly corresponding to that in which the mother has a scar. The advocates of the doctrine under discussion would quote this as an example of the inheritance of a deformity; and yet they would be entirely wrong, for scars and birthmarks represent two entirely different forms of tissue-change. When among the descendants of a man who suffered from any form whatever of mental disease, but only revealed the existence of that disease by the perversity of his actions after he had attained a certain age, there appears an inheritable affection of the central nervous system; or if we make a similar observation in regard to the appearance of myopia, we must not conclude from such observations that the disease first observed (in the ancestor) was strictly an acquired condition. The term *acquired*, in the sense in which it is employed in physical science, can only be applied to that which, in the course of the life of an individual, arises only through outward influences, but not to a peculiarity the first beginnings of which already existed in the germ, although the peculiarity itself may not have become recognizable until outside exciting causes had exerted their influence upon its development. Should there appear in a family hereditary mental disease or hereditary myopia, the first case may have already been due to a pathological condition of the germ, although no manifestations of the disease occurred until some of the outside influences of life called them into activity and so rendered the recognition of the pathological condition possible. Here, too, the particular pathological condition represents no true acquired disease.

There is still another thing that militates against the idea that an acquired pathological condition may be transmitted from parent to child; I refer to the simple consideration that the human race is exposed to so many injurious influences, and its individual members are so frequently sufferers from diseased conditions and mutilations, that, if this doctrine of the transmission of acquired pathological conditions were true, mankind would soon be in a condition of extreme suffering and misery, and would then perish. And this statement would still be true if only a portion of the acquired ailments were transmitted to the descendants; for, despite all their diseases and mutilations, human beings continue to bring descendants into the world.

The act of fructification—that is, the first step which leads to the production of a new individual—is accomplished by the copulation of the sexual nuclei—that is, of the ovum nucleus and that of the spermatozoön; and, according to the researches of the last decade, there is no longer any doubt that *these two nuclei are the bearers of the hereditary characteristics of the parents*, and that the individuality of the two copulating nuclei resides in their organization. It is impossible to imagine in what manner processes that take place in the body-cells can bring about in the sexual nuclei, which are lying inside of certain special cells in the sexual glands, such an alteration in their organization that from that moment onward they shall contain in potential form the acquired characteristics of the body, and shall transmit them, after copulation has taken place, to the descendants.

The question of the hereditary transmission of acquired characteristics has been much discussed in the last decade, and both anatomists and zoölogists, as well as pathologists, have taken part in the discussion.

Among the zoölogists, Weismann is the one who has especially defended the doctrine of the non-transmissibility of acquired characteristics, and has established it upon a scientific basis. According to his views, both those characteristics which belong to the species in general, and those which constitute the peculiarities of the individual, are supplied in potential form in the segmenting egg; and although later, through exercise, certain capabilities may apparently be acquired, nevertheless this can happen only in the case of those capabilities the first beginnings of which were already present in the germ or embryo, and consequently also in the body developed from it.

One can easily imagine that in the embryonal cells there are present two forms of plasma: the first, which is designed to build body-cells, and the second, which is intended for the construction of new embryonal cells, and which, earlier or later, after the beginning of the embryonal development, becomes separated from the first in the form of isolated cells. Accordingly, with the progress of segmentation and the development of the body, one part of the *germ-plasma* passes over in an unchanged form into the organism, and sooner or later manifests itself in the form of embryonal cells. It is supposable that all the differentiations which take place in the progress of the ontogenesis are dependent upon the chemical and physical molecular structure of the embryonal cells, and consequently that all *transmissible alterations* of the characteristics of the individual must arise from *primary alterations of the embryonal cells*. These transmissible alterations, therefore, are prepared beforehand by an alteration of the molecular structure of embryonal cells, and more particularly of the nucleus; an alteration which affects either the sexually differentiated cell-nuclei which have successfully copulated, or only the product of this union—the segmenting egg-nucleus.

Darwin in his time defended the opinion that acquired characteristics could be transmitted to the succeeding generations, and sought to make these phenomena intelligible by assuming that molecules from all the cells of the body contribute to the formation of the embryonal cells, and that, as a result of this, any alterations which take place in the organism can be transmitted to the embryonal cells. Notwithstanding this expression of his opinion, Darwin makes statements in his writings which do not agree with this opinion; indeed, some of them directly contradict this view.

It is not possible to speak further in this place upon the question of the transmission of acquired characteristics. Those who are more deeply interested in the subject will find it more fully discussed, at least in its relations to pathology, in various treatises which I have published in recent years.[*]

§ 32. As is shown in the explanations given in § 31, *inherited diseases are always such as arise in the first place from some internal predisposition —i.e., such as have developed from actual beginnings located in the germ or embryo—or at least they are diseases in which the element of predisposition is a congenital characteristic.* Conversely, the statement may be made that *all the normal or pathological qualities present in the embryo are transmissible.*

Consequently the question of the primary origin of inherited diseases coincides with the question concerning the nature of the causes of internal diseases—i.e., concerning the acquisition of those pathological characteristics which we regard, after they have made their appearance at some later date, as arising spontaneously, and as having their first traces in the germ or embryo.

The **first appearance of new pathological characteristics** which are hereditary may be connected with the fact that, as a result of **sexual procreation**—i.e., of the union of two sexual nuclei, of which the one is the bearer of the transmitted qualities of the paternal ancestor, the other of those of the maternal—**new variations** are constantly appearing, so that the fruit—that is, the child—never entirely resembles one parent; more frequently, in addition to the qualities which the parents offer, it also possesses new qualities. Even if we assume that the sexual nuclei sometimes contain in potential form exactly the same characteristics as those belonging to the parent out of whom they originated, the product resulting from the copulation of these nuclei would nevertheless present a certain degree of variation from the type of either parent. It may be said, however, that in a case like this the differences between the children of such a couple would be only slight. As a matter of fact, the different products of the same parents may vary to an immeasurable extent by reason of the fact that the sexual nuclei themselves contain a mixture of the characteristics inherited from the paternal and maternal ancestors, and that this mixture is never the same in the separate sexual nuclei of the individual.

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[*] Ziegler, "Können erworbene pathologische Eigenschaften vererbt werden und wie entstehen erbliche Krankheiten u. Missbildungen," *Beiträge von Ziegler*, i., 1886, u. *Verhandl. des V. Congr. f. inn. Med.*, Wiesbaden, 1886; "Die neuesten Arbeiten über Vererbungs- u. Abstammungslehre und ihre Bedeutung für die Pathologie," *Beiträge von Ziegler*, iv., 1888.

This statement is in harmony with the fact that the children in one family always present important differences in their bodily and mental characteristics, and with the further fact that a strong degree of resemblance is only observed in the case of twins that have been produced from one egg, or, in other words, only when the process of development has in both children started from the same act of copulation.

The **embryonal variations resulting from the mixture of two individually different hereditary tendencies** can find their expression in most varied qualities of the body and mind of the developing child. If these do not deviate in a marked degree from the characteristics which the different members of the same family are wont to show, the conditions are looked upon as normal, and generally receive no particular attention; but if, on the contrary, important differences in character are produced, the occurrence attracts greater attention, and, according to the value which it has for the individual, it is considered at one time as something favorable, at another as something unfavorable, something pathological. When small, weak parents beget children who grow to be big, strong men, or whose mental ability surpasses considerably that of the parents, it is regarded as a favorable occurrence. If a genius in any branch of human knowledge and skill should, as sometimes actually happens, develop suddenly in a family—i.e., without any hint of a particularly high mental development having been shown among the ancestors—the occurrence would attract universal attention and would be considered a fortunate event. But if, on the other hand, strong parents beget children that are weak or physically defective, or if their mental development remains considerably backward as compared with that of the parents, or if a complete arrest of development shows itself in some department of their mental faculties, *we call this newly appearing variation unnatural, pathological.*

If we take into account the experiences which the pathology of man and of animals furnishes, the assumption seems fully warranted that, among the **transmissible pathological conditions and tendencies,** very many, perhaps the majority, **are referable to a variation of the germ based upon the amphimixis.** This explanation is available, therefore, for the group of the hereditary diseased conditions and predispositions of the central nervous system, for hereditary myopia, for hæmophilia, for pigment-degeneration of the retina, and for polydactylism. If such abnormal characteristics repeatedly show themselves in the offspring of parents who are healthy and have healthy ancestors, one can conclude that the sexual nuclei of the parents, although individually normal, have through their union produced a pathological variation. This conclusion is substantiated when one or both parents produce normal offspring through copulation with other individuals.

Besides the variations which are the result of normal sexual reproduction, it is highly probable that pathological variations of the germ, which lead to the production of transmissible pathological characteristics, also owe their origin to the circumstance that **harmful influences** may have been exerted **upon the sexual nuclei or upon the segmentation nucleus,** or else that the **process of copulation**—i.e., the union of the sexual nuclei—may have been **disturbed** in some manner. The substance which acts prejudicially may be a product of the body, or it can come from without and at the same time also produce its harmful effect upon the body. Consequently in these cases one can speak of the *acquisition of a transmissible pathological peculiarity through some harmful influence emanating from the outer world.* But this expression is not intended to convey the idea, as many seem to believe, that the tissues of the body, under the influence of outside harmful agencies, first undergo certain alterations and then in some manner convey these alterations to the germ-cells. The proper explanation is, rather, that the injurious influence exerts its force directly upon the sexual nuclei or upon the segmentation nucleus, and here produces *some sort of a change*, which, at a later date, leads to a pathological transformation of the individual who is undergoing development from the impregnated egg. So far as the nature of the resulting pathological variation is concerned, it is a matter of no importance whether the somatic tissues are also subjected to alterations, and of what nature these are.

If a transmissible pathological characteristic has been produced, it may—provided it does not abridge life or prevent reproduction—actually be transmitted from parent to offspring, although this need not necessarily happen. The chances that this particular characteristic will be transmitted are greatest when the parents both possess it; when, for instance, both parents are affected with hereditary deaf-mutism or with near-sightedness. If the characteristic is wanting in one parent, there is a good prospect that a new germ-variation may be produced, in which the pathological characteristic fails entirely to manifest itself, and in later generations completely disappears. If there are several descendants, and if the tendency to this pathological defect has not entirely disappeared, it may show itself in only a few of the descendants, and then either in a modified or in an aggravated form. Finally, it sometimes happens that the characteristic remains latent in one generation—i.e., it does not extend beyond the sexual cells—and then reappears in the second.

There seems to me to be no doubt but that, through the copulation of two sexual germs possessing different hereditary tendencies, variations may be produced, and that among these there may be certain ones which we should consider as pathological. It is a more difficult thing to answer the question whether, besides these, there are not transmissible variations of a pathological character which owe their origin to influences that affect the sexual nuclei or the segmentation nucleus; and with what frequency, if the question be answered in the affirmative, these influences are exerted effectively. Weismann, according to the statements made by him in his most recent publications, is of the opinion that the first beginnings of the hereditary variations are not to be located in the amphimixis, but rather in the direct action of external influences upon the sexual nuclei. Starting out with the assumption that the variable cells or groups of cells derived from the germ (by him called *hereditary pieces* or *determinates*) are represented in the germ-plasma by special particles, which are formed by the grouping together of a number of *life-trophoblasts* or *biophores* (molecular groups which represent the smallest units of living matter), and which he calls *determinants* or *determining pieces*, he believes that he is warranted in ascribing the transmissible variation primarily to the circumstance that external agencies alter these groups of determinants and determinates contained within the nuclear chromatin, in such a manner that afterward the hereditary pieces or determinates which are dependent upon them also undergo a change. He believes that such an influence might be exerted by excessive nourishment of a determinant, causing it to assume a more rapid growth. Thus, for example, he believes that many congenital malformations—as, for instance, an increase in the number of fingers and toes—can be attributed to the overfeeding and consequent reduplication of the groups of determinants. The amphimixis has, according to Weismann, only a secondary influence on the production of a lasting variation, and this influence he defines to be the following: that it constantly, in some new manner, mixes the variations which are necessitated by the alteration of the determinants, and yet does not itself produce any *new* variations. "The alterations in character which the determinants undergo, through unequal influences of nutrition, constitute the material out of which, by means of amphimixis in connection with selection, the visible individual variations are developed; and then, by an increase of these variations and by their combining one with another, entirely new varieties are created."

I agree with Weismann to this extent: I consider that the appearance of new variations of a pathological nature is partly to be considered as resulting from changes which have been effected in the determinants contained in the sexual nuclei through the direct action of outside influences. I do not, however, believe that there is sufficient ground for attributing, as does Weismann, the development of new separate parts to the greater nourishment of individual groups of determinants. Such a dependence of the germ-plasma upon the surrounding nutritive material appears to me to be scarcely conceivable, and is in opposition to all the notions which we have hitherto held regarding the nutrition of cells. Accordingly, qualitative rather than quantitive alterations in the nutrient material would seem to be what is required in order to effect changes in the organization of the determinants; and, further, I believe that amphimixis holds not a secondary, but a primary position in the production of pathological variations, in the sense that it is itself competent to produce new variations. Finally, it seems to me that we cannot wholly set aside the hypothesis of Nägeli, according to which the idioplasma is capable of altering its own condition, from within outward, in certain fixed directions and according to certain fixed laws, and thus may produce new characteristics.

§ 33. In addition to the pathological conditions already enumerated, there are **a few infectious diseases** in which an **hereditary transmission** seems to occur. These are syphilis, smallpox, varicella, intermittent and recurrent fevers. At all events, in these diseases cases are sometimes observed in which a child, at the time of its birth or soon afterward, develops symptoms of the same disease from which the father or the mother had been suffering either at the time of procreation or during the period of gestation. This, however, is a phenomenon entirely different from that already spoken of as hereditary transmission.

Infectious diseases are caused by organisms which multiply in the body. The transmission of the disease to the child becomes possible only when the infecting organisms belonging to this particular disease either find their way into the sexual germ-cells and then also into the impregnated egg, or else pass from the maternal organism into the tissues of the child while developing in the uterus. The latter can occur as long as the child remains in the uterus, and it obliges us to assume that the infecting organisms pass through the decidual membranes and the outer coverings of the ovum—or, in the later periods of gestation, through the *placenta*—and thus are transported from the maternal to the child's organism. It is also possible that, where the parents keep up cohabitation for a certain length of time after impregnation has taken place, the micro-organisms which enter the vagina with the sperm may pass on into the uterus, and in this manner infect the already impregnated egg which is within that organ.

The transmission of bacterial infectious diseases to the embryo is beyond all doubt a possible thing. In the case of syphilis this may take place at the instant of impregnation as well as later during intra-uterine development, and the syphilis may be communicated to the child as well by the father as by the mother. In the case of smallpox, endocarditis, and scarlet fever, many instances of infection of the fœtus *in utero* have been reported; and, from recent observations and experimental investigations, there can no longer be any doubt that anthrax-bacilli, pus-cocci and pneumococci, and, under certain conditions, also typhoid-bacilli, can pass through the placenta to the fœtus. This can only occur when the bacteria gain an entrance into the maternal blood-channels of the placenta, and are capable of multiplying there, and then of penetrating into the fœtal vessels—a procedure which, according to Birch-Hirschfeld and Latis, is rendered possible chiefly by the damage done by the multiplying bacteria to the placental tissue, thereby enabling them to penetrate into the latter and to multiply within it.

There are therefore both **conceptional** and **intra-uterine placental infections**, which constitute a **pseudo-form of hereditary transmission**, in which the peculiar characteristics of the individual are not transmitted to the embryo, but instead an organized poison finds its way into the germ or into the already partially developed fœtus, where it undergoes further development and then calls into activity the same disease as that with which the parent is infected.

Our knowledge concerning the frequency of these occurrences is, unfortunately, still deficient. In the case of the most frequent of all chronic infectious diseases, tuberculosis, the rôle played by the disease proper is still by no means clear. Such a form of hereditary transmission is believed to exist by many persons in lepra, but it is denied by others; and in syphilis, where the frequency of its occurrence is not denied, our knowledge of the nature of the specific poison is still very meagre. In acute bacterial infections we know only of a transmission of the infection to the already developed embryo. How far the egg can be infected in the early stages of impregnation or at the actual moment of conception, without its further development being hindered thereby, is unknown.

If, during bacterial infections, infection occurs at the moment of conception, one must believe that the organisms belonging to the particular disease under consideration must have existed in the sexual glands at the time when the sexual cells were thrown off, then must have reached the egg at the moment when it became impregnated, or immediately afterward, and finally must have continued to live in it without hindering the further development of the egg. Then, besides, the assumption must be made that the Schizomycetes push their way into certain regions of tissues during fœtal development, and yet do not give rise to pathological processes until a later date is reached. Whether all these things are possible in certain infectious diseases further research must determine.

In a manner similar to that by which infections are carried to the fœtus can an *acquired insusceptibility to some particular disease* be transmitted from the mother to the child—that is, the antibodies (Ehrlich) present in the maternal organism can be transmitted to the fœtus. On the other hand, a transmission of immunity through the sperm, at the moment of conception, does not take place, and likewise there is no such thing as a genuine hereditary transmission of an acquired immunity. The experiments of Charrin and Gley, which are quoted in support of this idea, admit of a different interpretation.

SECTION III.

Disturbances in the Circulation of the Blood and of the Lymph.

I. General Circulatory Disturbances Dependent upon Changes in the Function of the Heart, Changes in the General Vascular Resistance, and Changes in the Mass of the Blood.

§ 34. It is by the work of the heart, in the rhythmical contractions of its auricles and ventricles, that the mass of the blood is kept constantly in motion. The blood within the elastic aorta, as it is driven toward the periphery of the body, meets, in the friction which exists within the innumerable divisions and subdivisions of the arterial system, a considerable degree of resistance; and this implies that there must be a relatively high pressure throughout the whole arterial system, a pressure which in the human arteria femoralis equals that of about 120 mm. of mercury. After passing through the capillaries the blood arrives in the veins with very little velocity, and stands in the veins under a very low pressure, which varies, however, according to the location of the vein, and is greatest where from the situation of the vein a blood-column of considerable height rests upon it. In the great venous trunks in the neighborhood of the thorax the pressure is generally negative, particularly during inspiration, as the thorax during this stage of respiration aspirates the blood from the veins lying without the chest. Only during forced expiration does the positive pressure within the veins rise somewhat higher.

At a given moment, the degree of pressure in the aorta, the mass of the blood remaining constant, is dependent upon the work of the heart and upon the resistance in the arterial system, and this in turn is dependent upon the area of the combined cross-sections of the blood-vessels, varying, as it does, owing to the elasticity and contractility of the arteries. In the corporeal circulation the tension of the arteries is very considerable; in the pulmonary circulation it is but slight, the blood-pressure in the pulmonary artery being only from one third to two fifths that in the aorta. Both the heart and the arteries are under the influence of the nervous system which regulates their action.

The function of the heart consists in rhythmical contractions of the heart-muscle, and its normal efficiency presupposes that the heart-muscle as well as the heart-ganglia is sound. Every lesion of the heart, therefore, inasmuch as it diminishes the contractility of the heart-muscle and disturbs the action of the cardiac ganglia, in just so far as the diminution in the efficiency of certain parts of the heart-mechanism is not compensated by increased activity of other parts, will **impede the effective working of the heart.**

In many cases where the efficiency of the heart has become impaired, certain anatomical changes, such as fatty degeneration and cell-disintegration, can be demonstrated; in others microscopic examination fails to reveal any anatomical differences, particularly in cases where the diminution of efficiency has resulted from the exhaustion consequent upon over-exertion. This may occur either when—as, for instance, in cases of febrile temperature—for a considerable length of time, the heart performs its function under unfavorable conditions, though at no time forced to work more than slightly beyond its normal rate; or when, for a brief period, the demands upon the heart become excessively severe. Moreover, either trophic disturbances, or the toxic condition accompanying the febrile infectious diseases, or sudden diminution of the blood-supply from obstruction of a coronary artery, may, under certain circumstances, bring about heart-failure within too short a time to allow anatomical lesions of the muscular tissue to become recognizable. A further obstacle to the working of the heart is occasionally caused by adhesions of the surface of the heart to the pericardium and to contiguous portions of the lung, inasmuch as the heart is thereby hindered in the amplitude of its contractions.

Through the serous collections in the pericardium which occur during the course of certain diseases, through pronounced degrees of thoracic deformity, through high convexity of the diaphragm, the ready enlargement of the heart during diastole may be impeded, and thereby the free afflux of blood from the venous system be interfered with to such an extent that ultimately the blood is but scantily furnished to the ventricles. Should rents or distortions of the flaps of the valves occur, or adhesions between them arise in consequence of pathological processes, or should the valve-flaps, on account of dilatation of the heart, become relatively too short, then there will be developed at the orifices of the ventricles the conditions which are known as insufficiency and stenosis. The former of these is a condition where a valve, during the contraction of the auricle or ventricle next ahead of it, fails to completely close its proper orifice; the latter a condition where, during the contraction of the auricle or ventricle behind it, the ostium fails to become sufficiently widely open. The effect of any stenosis is an impediment to the advancement of the blood; in the case of aortic or of pulmonary insufficiency the blood escapes during the ventricular diastole from the great vessels back into the ventricles; in that of mitral or of tricuspid insufficiency the ventricular systole forces the blood back into the respective auricles.

Finally, clots are not infrequently formed in the heart, and these, under certain circumstances—namely, when they lie in proximity to the ostia—on the one hand interfere with the closure of the valves, and on the other hand cause a narrowing of the orifice.

The universal operation of all the above-mentioned pathological conditions of the heart is to produce the following results: **the efficiency of the heart's function becomes impaired,** too small a volume of blood is in a given time delivered to the arterial system, and consequently the blood-pressure in the aorta falls, the velocity of the blood-current is lessened, and the blood collects more and more in the venous system, while the pressure in the veins rises. There is consequently an *incomplete filling of the arteries* throughout the whole body, varying, indeed, in the several parts according to the degree of contraction taking place in individual groups of arteries, while both veins and capillaries are, on the other hand, overfilled with blood. The condition becomes one of general *venous hyperæmia*, which may in some parts become so great that, on account of the engorgement of the capillaries with venous blood, the tissues acquire a *livid, cyanotic appearance.* When the difference between the pressure in the arterial and that in the venous system reaches a certain minimum, the circulation is arrested, while the right auricle and ventricle are distended with blood.

Should the contractions of the heart have become, from any cause, feeble and incomplete, then the pulse-wave also is small. Should the rate of the heart-beats become slower, the arterial system during the interval between two systoles tends to empty itself more than normally.

If the impairment of cardiac efficiency is essentially dependent upon imperfect function of the left side of the heart, as is the case, for instance, in valvular lesions of the left heart, then the disturbance of the circulation first becomes manifest in the arterial portion of the corporeal and in the pulmonary circulation.

With stenosis at the aortic orifice, the arteries, if the heart's action remain unchanged, fill but slowly and incompletely (pulsus tardus). With insufficiency of the aortic valves, a normal or even an increased volume of blood is thrown into the arteries (pulsus celer); a portion of this, however, flows back into the ventricle during diastole. In both cases an over-distention of the left ventricle becomes more and more established, and eventually it leads to an interference with the emptying of the left auricle, and thereby to over-accumulation of blood in that chamber and subsequently in the pulmonary veins. Owing, however, to the low pressure in the pulmonary circulation, the blood is readily dammed back upon the right ventricle, and the tendency to blood-stasis, extending beyond this, reaches to the right auricle and finally to the venous system throughout the body.

A similar effect upon those portions of the circulatory apparatus which lie back of the left auricle is caused by valvular lesions at the mitral orifice, as in these cases also there is blood-stasis in the pulmonary circulation and a rise of pressure as well in the pulmonary veins as in the pulmonary arteries; while the left ventricle either receives too small a supply of blood (stenosis) or during its contraction drives back a portion of its contents (insufficiency) into the auricle.

In valvular lesions at the orifices of the right heart, the damming back of the blood is limited to the veins of the corporeal circulation, while in the pulmonary circulation both velocity and pressure are diminished. Ultimately the pressure falls in the aortic system also, as the left side of the heart receives a diminished supply of blood.

Damming back of the blood in the great veins of the body often gives rise to *venous pulsation* in the neighborhood of the thorax, as in these veins waves moving toward the capillaries arise, which overcome and pass the venous valves, and in particular the valve in the bulb at the junction of the internal jugular and subclavian veins. The cause of the venous pulsation is the failure of the valves in the veins to close. In case of imperfect function of the valve at the bulb this pulsation may be observed in a slight degree even during normal action of the heart; but when there is distention of the veins, and particularly when there is tricuspid insufficiency, the pulsation is far stronger and is traceable much farther toward the periphery. If the tricuspid still close completely, the venous pulsation is then only the expression of the rhythmical recurrence of an interruption to the outflow of the blood from the veins; if the tricuspid be incompetent, blood is driven back upon the veins during the contraction of the right ventricle.

When certain of the chambers of a heart affected with valvular lesions become distended with blood, the muscular walls of these chambers may, by an increased activity, *compensate, to a certain degree, for such valvular defects.* In course of time an increase in volume—a *hypertrophy of the heart-muscle*—follows, and enables the heart for an indefinite period to meet the increased demands upon it. Such compensation, however, frequently becomes insufficient, with the result that the pressure permanently remains abnormally low in the aorta and abnormally high in the veins. There is, at the same time, the danger that the heart-muscle may tire in time, or that a very slight illness may render the heart insufficient. Thus, for example, a prolonged quickening of the heart's action, in that it abbreviates the diastolic rest of the heart-muscle, may suffice to bring about fatigue and insufficiency of the heart. Cardiac arrest finally follows, with great accumulation of blood in the heart from sheer inability of the organ to drive onward the mass of blood flowing into it.

Quickening of the heart's action—that is, increase in the frequency of the contractions, each being strong and full—causes a rise in arterial blood-pressure and an increased velocity of the blood-current. When increased demands are repeatedly made upon the left side of the heart—as frequently happens in consequence of severe bodily labor, of a life of excitement, or of abnormal irritability of the cardiac nerves—the left ventricle may become hypertrophied and may act permanently with increased force. Inasmuch as from quickening of the blood-current the right cavities of the heart receive a larger amount of blood during diastole, the hypertrophy of the left side of the heart is ordinarily accompanied by a similar condition of the right ventricle.

Lessening of the mass of the blood, or **general anæmia**, from hæmorrhage, leads to a temporary lowering of pressure in the aorta; but if the loss of blood was not excessive, this pressure presently rises again as the blood-vessels adapt themselves to their new conditions, and, as a consequence of the stimulation of the vaso-motor centre through local anæmia, display a higher degree of contraction. Under normal conditions a speedy increase in the mass of the blood takes place through absorption of fluids, and later on through regeneration of the blood proper. Similarly, the arterial pressure is lowered and the blood-current slowed in **anhydræmia**—i.e., in diminution of the fluid portion of the blood. After severe hæmorrhage the arterial pressure remains low for a considerable period of time, the circulation being slowed, and the pulse, because of the stimulation of the vagus-centre (Cohnheim), being frequent and small.

In case of long-continued diminution of the mass of the blood—that condition which is known as **chronic anæmia**, and which appears under many different circumstances (see Section I. of the Special Part)—the vascular system is but imperfectly filled, the blood-pressure is lowered, and the blood-current is slowed. Both the heart and the blood-vessels adapt themselves to the new conditions and become diminished in volume. With great deficiency in hæmoglobin, degeneration of the heart-muscle—particularly fatty degeneration—frequently takes place.

In the lower animals **increase in the volume of the blood** through injection of blood or of salt-solutions into the vessels is followed by only a temporary increase in the blood-pressure and in the velocity of the blood-current (Cohnheim). A return to the normal follows, partly through the dilatation of a portion of the vascular system, particularly in the abdomen, partly through the elimination of the surplus from the vessels. If the mass of the blood, as a result of some special diathesis or of high living, come to stand in abnormally high proportion to the weight of the body, if there exist a **permanent condition of plethora,** the pressure in the aorta will then be permanently raised in consequence, the task of the heart will be permanently increased, and a corresponding condition of *hypertrophy* will ensue.

§ 35. **Increase of general vascular resistance** occurs as well in the corporeal as in the pulmonary circulation, and results in increased pressure behind the point of increased resistance, and diminished pressure ahead of it.

In the **corporeal circulation** the hindrance may lie either in the main vessel, the aorta, or else in the arterial branches, whose degree of contraction maintains and governs the pressure in the aorta. General vascular contraction involving the areas supplied by a large number of arteries, and sufficiently well marked to increase the blood-pressure, is generally but a temporary disturbance which passes off with the relaxation of the arterial excitement; nevertheless a permanent increase in blood-pressure does occur, accompanied by hypertrophy of the left ventricle, and it cannot well be accounted for otherwise than as the result of a contraction of the lumen of the smaller arteries. Temporary vascular contraction and increase of pressure occur particularly through overcharging of the blood with carbonic acid; permanent increase of pressure in the aorta, on the contrary, is a result of chronic kidney-disease in which the secreting parenchyma of the kidney is destroyed, with which destruction the increase of blood-pressure stands doubtless in direct relation. Inasmuch, however, as that portion of the vascular system which in this case is cut off is far too inconsiderable to cause, by itself, an increase of pressure throughout the whole aortic system—since the blood-vessels leading in other directions might well become correspondingly relaxed—we are compelled to assume that in kidney-disease other obstacles to the circulation are developed throughout more considerable vascular areas, and these we most naturally seek in that apparatus which normally serves to maintain the aortic pressure at its proper level—namely, in the smaller arteries distributed throughout the body. Whether we have to do with reflex stimulation from the kidneys through the nerves, or whether with retained urinary ingredients working upon the vaso-motor centres or directly upon the walls of the vessels, or whether with the heart driven to more forcible action through stimulation of its nerves, we are not at present able to determine.

Increase of pressure in the aorta may result from stenosis of this vessel, which has occurred in rare cases at the isthmus,* or from congenital narrowness of the whole aorta, or from large aortic thrombi, or from an advanced stage of disease of the vessel-wall, with the intima consequently rough and lumpy and the whole vessel rigid, inelastic, and unyielding, or, finally, from a general dilatation of the vessel, whereby counter-currents are formed in the passing blood-stream.

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* The "isthmus" of the aorta, I suppose, is the point where it pierces the diaphragm. I am not familiar with the term, and I am unable to find any reference to it in Quain's or Henle's Anatomy, or in the Medical Dictionaries of Kraus and Foster.—TRANSLATOR'S NOTE.

Diminution of the total resistance in the corporeal circulation is possible through relaxation of the tone (muscular contraction) of a large part of the arteries, an event which follows when the vaso-motor centre is paralyzed or when the cervical cord is divided or partly destroyed by any other process. As the blood, in this case, flows too quickly from the arteries over into the veins, an equalization of the pressure between arteries and veins follows, the blood-current is slackened, the heart receives during diastole an insufficiency of blood, and the circulation may finally come to a standstill.

Increase of the resistance in the pulmonary circulation arises most frequently in consequence of disease of the lungs and of the pleura. Adhesions of the pleuræ, as well as curvature of the spine, may be a cause of such increased resistance, in that they cause displacement of the lungs and hinder the respiratory movements of the chest-wall and thereby cause the withdrawal of an efficient aid to the circulation. Of great influence, moreover, are diseases which, like emphysema, contraction, and other disturbances of the lungs, lead to impermeability of a portion of the pulmonary capillaries; and, furthermore, the same is true of compression of the lungs by pleural exudations, and of compression of the pulmonary arteries by aortic aneurism or by tumors.

If the obstacle be but inconsiderable, the blood can still make for itself a free passage to the left side of the heart without increase in the blood-pressure; only the velocity of the flow is increased through the channels that still are open. Greater obstacles cause increase of pressure in the pulmonary artery and in the right side of the heart, and, if the condition continue for a long time, they may cause hypertrophy of the right ventricle through increased exertion of the heart. This can only come to pass, however, when the nutrition of the heart-muscle is meantime maintained, and when the mass of the blood is not diminished to correspond with the diminution in the area of the pulmonary tract. If the right side of the heart do not succeed in overcoming the obstacles in the pulmonary circulation, the blood is then dammed back upon the right side of the heart and eventually upon the venous system.

Rise of the pressure in the right half of the thorax hinders the influx of the venous blood into the right auricle, and causes an accumulation of blood in the veins of the whole body.

The observation that cardiac hypertrophy results from different renal diseases has been differently explained by different authors. Some seek the cause of the phenomenon in an increase in the mass of the blood (Traube, Bamberger); others (Senator, Ewald) think it dependent upon a change in the composition of the blood; others, again (Gull and Sutton), ascribe it to a wide-spread alteration in the walls of the smaller arteries. Buhl attributes it to overnourishment of the heart. The final result of recent investigations places beyond doubt the dependence of the cardiac hypertrophy accompanying renal disease upon an increase of arterial pressure. According to Cohnheim, the proportion of unexcreted waste products in the blood is the determining factor of the degree of contraction of the renal arteries. In renal disease the same amount of blood is carried to the kidneys as when the kidneys are sound. If now an abnormal resistance is introduced beyond the renal arteries, the arterial pressure rises.

According to my opinion, the increase in aortic pressure is most readily to be explained by the increase in the resistance throughout the small arteries of the whole body. If cardiac hypertrophy follow a primary renal affection we must suppose that on account of the latter the resistance outside of the kidneys is also increased. This is caused by contraction of the smaller arteries, and this in turn must be brought about either by the direct action of retained waste products upon the arterial walls, or else by reflexes starting from the kidneys, or, finally, by irritation of the vaso-motor centres. It is also possible that the heart may by these same means be stimulated to increased exertion.

According to the observations of Löwit, compression of the trunk of the aorta sometimes does and sometimes does not cause an increase of blood-pressure in the pulmonary artery. Löwit considers this rise in pressure to be independent of the stasis in the left auricle. In his opinion, the rise does not result from a damming back of the blood from the left on to the right side of the heart, but much rather is caused by an increased afflux of blood to the right side of the heart, which is in its turn brought about by a relaxation of the contracted arterioles due to cerebral anæmia. The correctness of Löwit's observations cannot be called in question, and his interpretation also is to be accepted, but it is by no means to be considered as showing that in cases of permanent obstructions in the corporeal circulation, or in the left side of the heart, which cause a setting back of the blood, such a damming back of the blood does not reach the pulmonary artery and by way of the lungs extend beyond it into the right side of the heart.

II. Local Hyperæmia and Local Anæmia.

§ 36. To the blood is assigned the function of carrying nourishment to all the organs and tissues of the body. The cells and cellular structures of which the various tissues are composed are able to maintain their existence but a short time without the advent of fresh supplies of nutritive material, and for this reason most of the tissues are provided with blood-vessels, and such tissues as lack them are placed in the most intimate connection with vascular structures.

The demands of the various tissues for blood are not always uniform, and there is consequently in the various tissues an alternating increase and decrease in the afflux of blood, and at the same time in the amount of blood contained within the organ or tissue at a given moment. An organ richly filled with blood is designated as **hyperæmic**; if containing but little blood it is said to be **anæmic.**

The regulation of the volume of blood which an organ receives under physiological conditions is brought about by a change of the resistance in the afferent arteries, and this change is passively effected by variations in the calibre of these vessels. Inasmuch as the mass of the blood in the body does not suffice to fill all the vessels at once, an extra supply for one organ becomes possible only by diverting the blood from other directions. The change in the calibre of an artery is determined, aside from the blood-pressure, by the elasticity of its walls and by the degree of contraction of its organic muscular fibres. These fibres are the regulating agents, and their action is dependent partly upon influences acting on them directly, partly upon nervous impulses from the intravascular plexuses and from the vaso-motor centres in the spinal cord and in the medulla oblongata; some stimulating and others inhibiting the muscular action.

When the variations from a mean in the blood-supply of a part overstep the physiological limits, or when these variations arise without their physiological causes, or when the condition is unduly protracted, we then call the state one of **pathological hyperæmia** or of **pathological anæmia.** These conditions are only in part caused by the same governing mechanism which determines the normal blood-supply of an organ.

§ 37. **Hyperæmia** of an organ is caused, under pathological conditions, either by an increase of the arterial supply or by an obstruction and hindrance to the venous outflow, and we distinguish, accordingly, an *active* or *congestive* (arterial) *hyperæmia* and a *passive* or *stagnation* (venous) *hyperæmia.* **Active hyperæmia** arises from an *increase of the afflux of blood* (*congestion*), and is either *idiopathic* or *collateral.* The first of these plays the more important rôle, and depends upon a relaxation of the muscular tunics, which is caused either by *paralysis of the vasoconstrictor nerves* (*neuroparalytic congestion*), or by *stimulation of the vasodilators* (*neurotic congestion*), or by direct *weakening* or *paralysis of the muscles* (as, for instance, through heat, bruising, the action of atropin, brief interruptions of the blood-current), or, finally, by *diminution of the pressure bearing on the vessels.* Collateral hyperæmia is merely the result of a diminished flow of blood to other parts. It arises first in the immediate neighborhood of the parts whose blood-supply is lessened; afterward the blood may be driven also to such other more remote organs as may require it.

Active hyperæmia is accompanied by more or less *marked redness* and *swelling of the part*—changes which are quite striking in tissues that are rich in blood-vessels. The blood flows through its widened channels with increased velocity and lends to the tissue the color of arterial blood. Tissues situated superficially, and thus exposed to cooling, grow warmer, in consequence of the more active passage of blood through them than through the surrounding parts less generously supplied with blood.

Passive hyperæmia is a consequence of *retardation* or *obstruction of the flow of blood in the veins.* A *general tendency to blood-stasis throughout the corporeal circulation* follows directly whenever feebleness of the heart's action, insufficiency or stenosis of the cardiac valves, or obstructions in the pulmonary circulation impede the emptying of the large veins into the right side of the heart. In the pulmonary circulation it is more particularly aortic or mitral lesions, or weakness of the left side of the heart, less frequently obstacles in the arterial portion of the corporeal circulation, which, by obstructing the outflow of blood from the lungs, lead to a pulmonary stasis; the latter not infrequently reaching a degree that makes the damming back of the blood appreciable in the right side of the heart as well as in the veins of the corporeal circulation (cf. § 34).

Local stasis may follow directly from the fact that the progress of the blood through the veins lacks the continued support of the action of the muscles and of the aspiration of the blood through the inspiratory enlargement of the thoracic cavity. The defection of the first of these auxiliary forces becomes most obvious in the area of distribution of the inferior vena cava; as, for instance, in subjects who live continuously sedentary lives, or who stand a great part of the time without active bodily movements, so that the task of emptying the deep-seated veins into the trunk of the vena cava falls almost exclusively upon the forces inherent in the walls of the veins—namely, their elasticity and contractility—these forces being insufficient to drive onward the column of blood which presses against the walls of the vessel. An inadequate aspiration through the respiratory movements makes itself felt when respiration is interfered with by inflammation or other disease processes in the lungs or the pleura.

A further cause of local passive hyperæmia consists in the narrowing or closing of particular veins, as occurs in compression, ligation, the formation of thrombi (§ 39), and the invasion of the veins by neoplasms. The pregnant uterus, for example, or a pelvic tumor may compress the veins of the pelvis, a thrombus may choke the cerebral sinuses or the femoral or the portal vein, or a sarcoma of the pelvis may grow into the great pelvic veins.

Should any single vein become occluded by any of the above processes, or be ligated during operation, the effect of such occlusion is often very inconsiderable, inasmuch as the vein in question may have free and manifold connection with other veins, so that no considerable obstacle is created to the progress of the blood. If, on the other hand, the occluded vein has no auxiliaries, or if these are insufficient for the passage of the blood—as, for instance, is the case with the radicles of the portal vein, with the sinuses of the dura mater, with the femoral or with the renal veins—then a greater or less degree of stasis occurs in the area of distribution of the vein affected.

The effect of the obstacle to the circulation shows itself first in the portion of the vein which lies between the obstruction and the periphery, the blood-current in this part becoming slowed or entirely checked, while at the same time, through continued afflux of blood from the capillaries, a progressive filling and stretching of the vein follows. If through the compensatory action of the elastic and contractile vessel-wall, in yielding more and more to the pressure, the obstruction can be overcome, the circulation will remain intact, and, through such channels as it still finds open to it, the blood will flow on to the heart; and oftentimes under these circumstances the small veins which have to perform this increased labor become gradually much dilated, and are eventually converted into veins of large size. If the obstruction cannot be overcome, and if no communicating vessels capable of dilatation are at hand, the circulation will be arrested, and a condition of complete stasis (§ 42) or of thrombosis (§ 39) will be brought about in the area of distribution of the obstructed vessel.

If the arrest of the blood in the area of distribution of a vein extends to the capillaries, so that these become distended with blood, this will impart a *reddish-blue, cyanotic hue* to the surrounding tissues, and a certain amount of *swelling* will take place in them.

Both active hyperæmia and passive hyperæmia, observed during life, may take on quite a different appearance after death, and may even, in not a few instances, entirely disappear. This is especially the case with active hyperæmia of the skin and sometimes with that of the mucous membranes, and it is dependent upon the fact that the tissues, put upon the stretch by the dilatation of the capillaries, contract down upon the latter after the ceasing of the circulation, and by their counter-pressure drive the contents of the capillaries on into the veins. Tissues which may have been reddened during life may accordingly appear pale after death. As converse to this, other tissues which during life were pale, or at least showed no particular redness, may take on, after death, a reddish-blue color. This occurs especially upon the sides and back of the trunk
parts happen to be uppermost) and upon the back of the
osterior aspect of the extremities of a cadaver lying face
be explained by the fact that after death the blood

sinks to the most dependent parts, and fills not only the veins, but finally also the capillaries. The phenomenon is known as *post-mortem hypostasis*, and the spots are known as *death-spots* or *livid spots* (*livores*). They appear as early as three hours after death, and their number and size are proportionate to the amount of blood contained in the skin and in the subcutaneous tissues at the moment of death.

In the internal organs post-mortem hypostasis is particularly apparent in the pia mater, whose dependent veins are generally more completely filled with blood than those lying above them. In the lungs we get, through the settling of the blood, engorgement not only of the veins, but also of the capillaries.

Whenever during life, on account of cardiac insufficiency, the general circulation is imperfect and partial stagnation of the blood follows, the blood often collects in a similar way in the dependent portions of the body, partly because it is not driven out of them, and partly because it sinks into these parts from those situated on a higher level. This phenomenon, likewise designated as *hypostasis*, is particularly observed in the lungs (hypostatic congestion).

For observing the circulation during life, and its behavior under changes of velocity and pressure, we make use of either the tongue or the web of the foot of a curarized frog * properly spread on an object-holder. A very simple expedient, for instance, is to draw out the tongue and spread it over a cork cemented upon the object-holder, and fasten it there with pins. With a normal circulation both the pulsating arterial current and the steady-flowing venous current exhibit a marginal zone of blood-plasma. If by ligation of the efferent veins we induce a partial stagnation the flow becomes slowed, the clear marginal zone of blood-plasma disappears from the veins, and both veins and capillaries become distended with accumulated red blood-corpuscles. After a certain time the tongue begins to swell through infiltration with transuded fluid.

The frog's tongue and the web of the frog's foot are also well adapted to the study of the circulation during active hyperæmia and during anæmia.

According to the investigations of Landerer,† the wall of a capillary vessel embedded in the tissues supports only from one third to one half the blood-pressure. The remainder is borne by the surrounding tissues, which afford an elastic resistance and so maintain the tension which is necessary to keep the blood in circulation. In active hyperæmia as well as in passive hyperæmia, the tension of the tissues and the pressure upon them are increased; in anæmia both are diminished.

§ 38. **Localized anæmia** or **ischæmia** is a condition wherein certain tissues contain but a small amount of blood; it is always the result of a diminution in the afflux of blood. If the total bulk of the blood is normal, then the cause of the ischæmia is purely local; if there is an insufficient quantity of blood in the whole vascular system, the local insufficiency may partly depend upon that.

The *pathological diminution in the afflux of blood* to an organ is sometimes merely the result of an unusual *increase in the normal resistance* of the arteries—that is, of a contraction of the muscular tunics. In other cases *abnormal obstructions*—such as compression of the arteries, narrowing of the arterial lumen through pathological changes in the vessel-wall, deposits on the internal surface of the vessels, occlusion of the vessels by emboli (cf. § 18), etc.—act as hindrances to the blood-current.

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* Cohnheim, *Virch. Arch.*, 40. Bd.

† "Die Gewebsspannung," Leipzig, 1884.

The immediate consequence of the *narrowing of an artery* is always slowing and diminution of the stream beyond the point of constriction. *Complete occlusion* of an artery brings the circulation beyond the obstruction to an immediate standstill. If, back of the point of constriction or occlusion, the artery be provided with connecting branches of relatively considerable size—so-called *collateral arteries*—the disturbance of the circulation is abated by an increased flow through the collateral vessels; and the larger and the more distensible these are, the more complete the restoration of the circulation. If the constricted or occluded artery possess no communicating branch in its area of distribution—if it be a so-called *terminal artery*—the slowing or the arrest of the circulation beyond the point of obstruction or of occlusion cannot be immediately done away with, and the area supplied by this vessel becomes presently partly or completely emptied of blood, as, through the contraction of the arteries, and through the pressure of the tissues upon the capillaries and veins, the blood is more or less completely forced out of the area of distribution of the artery in question. Frequently, however, after a short time has elapsed, an afflux of blood comes from neighboring capillaries.

When the current and the pressure beyond a *constricted point* have sunk below a certain minimum, little by little the driving force becomes less and less able to push along the mass of the blood. The red corpuscles, particularly, cease to move, and collect in the veins and capillaries, and as a consequence *the area supplied by the artery in question becomes filled with blood once more;* only not with circulating, but with stagnant blood. *The same thing occurs when, a terminal artery being completely occluded, the blood oozes into the affected area, under minimal pressure, through arteries incapable of adequate enlargement, or merely through communicating capillaries.* An accumulation of blood within the anæmic area may also occur by reflux from the veins. This occurs when the intravascular pressure within this area has sunk to nothing, and when neither the weight of the blood nor the venous valves oppose the reflux of the blood.

A further cause of anæmia in an organ may be the abnormal congestion of other organs, as in that case the total mass of the blood would not suffice to supply the remaining organs adequately. Anæmia from this cause is called *collateral anæmia.*

All *anæmic tissues* are characterized by *pallor.* They are at the same time flabby, not turgescent, and the color proper to each appears distinctly under these circumstances.

The **significance of a condition of ischæmia** lies especially in the fact that, on account of the need of the tissues for a continuous supply of oxygen and other nutritive elements, the continuance, for a certain length of time, of the condition of imperfect blood-supply brings about *tissue-degeneration* (cf. § 3). Complete arrest of the blood-supply leads in a short time to *death* of the tissue involved. If blood come to flow anew among the degenerated and dying tissues in the area of distribution of an obstructed vessel, and stagnate there, extravasation of blood into the tissues may follow, and a *hæmorrhagic infarct* (cf. § 47) be formed.

The rapidity and completeness with which a *collateral circulation* may be developed after the occlusion of an artery depend upon the size and distensibility of those vessels which are in communication with the area which has become ischæmic. If these are numerous and distensible, the ischæmic area becomes very soon irrigated with an approximately normal volume of blood. If this is not the case the disturbance of the circulation corrects itself much more slowly, and stasis and increased pressure are found to extend farther back from the point of obstruction toward the heart, so that the collateral circulation becomes established through vessels situated farther back on the course of the blood, i.e., nearer the heart. In the further course of the process of reëstablishing the circulation, the increase in the volume and velocity of the blood-current remains confined to such vessels as communicate with the area deprived of its natural blood-supply—that is, confined to the capillary and arterial anastomoses; and here this increase becomes permanent, and leads in turn to a permanent distention of the vessels of the part, and at the same time to a substantial increase in the vascular walls, not only in thickness, but, as becomes evident from the crooking and twisting of the vessels, in length also. According to Nothnagel, in rabbits the phenomenon of the increase in thickness of the walls of the anastomotic vessels may be demonstrated about six days after the ligation of an artery; and after the ligation of vessels of some size, the small arteries which carry on the collateral circulation become transformed, in the course of a few weeks, into quite capacious, thick-walled arteries.

III. Coagulation, Thrombosis, and Stasis.

§ 39. Upon the death of the individual, the blood lying in the heart and in the great vessels generally coagulates in part, sooner or later, and thence arise those formations known as **post-mortem clots.** If the clotting occur at a time when the red blood-corpuscles are still evenly distributed in the blood, and the whole mass of the blood become coagulated, the clots form dark-red masses—a condition in which the blood is termed *cruor.* If before coagulation, through the settling of the red corpuscles, the mass divide itself into a substratum rich in red blood-corpuscles and an upper fluid layer containing none and consisting exclusively of the plasma; and then if the latter coagulate, there will be formed soft gelatinous lumps, and also fibres, light yellow in color, elastic, with a

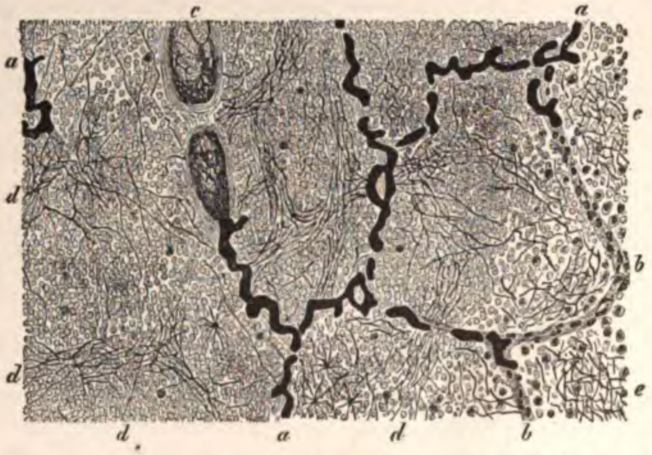

FIG. 6.—Part of the border of a recent hæmorrhagic infarct of the lung. *a*, Interalveolar septa without nuclei, containing capillaries filled with deep-violet thrombi of homogeneous appearance; *b*, Septa showing nuclei; *c*, Vein containing a red thrombus; *d*, Alveoli distended by a firm blood-clot; *e*, Alveoli filled with serous fluid, fibrin, and leucocytes. (Specimen hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 100 diameters.)

smooth surface, and not adherent to the vessel-wall, which are designated as *lardaceous clots* or as *fibrinous deposits.* Through the inclusion of red blood-corpuscles in these formations, they may exhibit in parts a red or reddish-black color; but when an unduly large proportion of leucocytes are present, the color at such spots will border on white.

If blood be drawn from an artery or a vein and received into a vessel, within a short time *coagulation* will occur, transforming the whole into a soft coherent mass. If freshly drawn blood be beaten with a solid body, in a short time stringy *fibrin* will be separated from the surface of the blood. *If within the body blood be extravasated in considerable quantity into the tissues*—for instance, into the pericardium or into the lungs—*coagulation* may occur here likewise, and among the red blood-corpuscles stringy masses are formed (Fig. 6, *d*, *e*), whose fibres run in the most varying directions, crossing one another continually, and frequently also proceeding radially from a central point.

The **coagulation of the blood** is a process difficult of chemical interpretation, and in spite of numerous investigations we have not succeeded in explaining this enigmatical phenomenon. We know, however, that for its occurrence the presence of a *fibrinogenic substance*, of a *ferment*, and of certain *salts*, especially *calcium salts*, is indispensable, and that the fibrinogenic substance is an albuminoid body, belonging to the class of the *globulins*, which is present in the blood, while the ferment is probably derived from the white (possibly also from the red) corpuscles of the blood, which either are dissolved in the blood-plasma, or yield to it certain constituents of their mass. According to A. Schmidt, by means of the fibrin-ferment a very bulky albuminoid body is formed, in a way still obscure, out of the globulins preëxisting in the alkaline solution, which body is precipitated by the calcium salts present in the plasma; and in the process of coagulation we must recognize two stages—to wit, the stage of the production of the ferment and the stage of the fermentative action or coagulation proper. According to Pekelharing, on the other hand, the fibrin-ferment is itself a calcium compound which has the power of carrying lime over to the fibrinogen, whereby from the soluble fibrinogen an insoluble albuminous compound is formed, containing calcium, which body is fibrin.

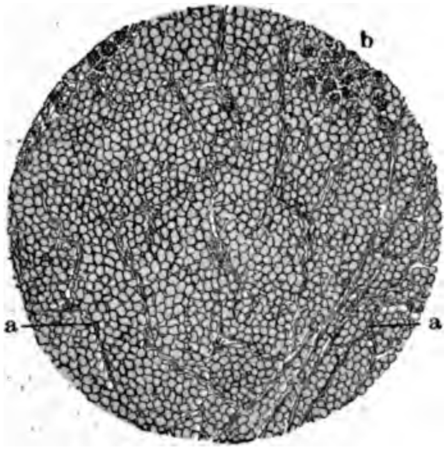

FIG. 7.—Section through a red thrombus formed in one of the muscular veins of the thigh after occlusion of the femoral vein. *a*, Fibrin threads; *b*, Leucocytes and granular bodies. (Specimen hardened in Müller's fluid, and stained with hæmatoxylin. Magnified 250 diameters.)

If coagulation of the blood within the heart and the vessels take place during life, or if a solidifying mass separate from the circulating blood, this process is called **thrombosis** and its product a **thrombus**.

If coagulation or **thrombosis occur in a mass of blood deprived of motion**, there is formed a **dark-red thrombus** (Fig. 6, *c*, and Fig. 7), which, like the reddish-black post-mortem clots, or like the coagula of extravasated blood (Fig. 6, *d*), contains all of the red blood-corpuscles; the precipitated fibrin forming granules (*b*) and fibres (*a*).

Immediately after its formation the thrombus is soft and rich in the fluids of the blood; later it becomes tougher, denser, and drier as the fibrin contracts and presses out a portion of the fluid. At the same time it becomes paler, brownish red or rust-colored, inasmuch as the blood-pigment undergoes changes similar to those in extravasation.

Fig. 8.

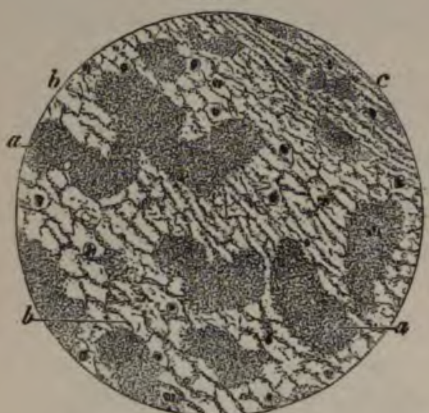

Fig. 9.

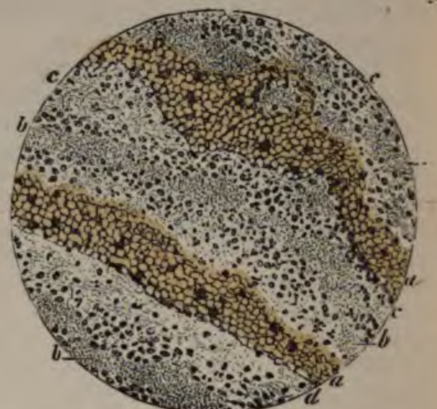

FIG. 8.—Section of a white thrombus extending through the vena cava inferior, and containing but few cells. *a*, Granular mass; *b*, Granular and stringy fibrin in retiform arrangement; *c*, Threads of fibrin in parallel arrangement. (Preparation stained with hæmatoxylin. Magnified 200 diameters.)

FIG. 9.—Section of a mixed thrombus of the aorta, rich in cells. *a*, Red blood-corpuscles; *b*, Granular mass; *c*, Retiform disposition of fibrin with numerous leucocytes; *d*, Threads of fibrin in parallel arrangement. (Preparation stained with hæmatoxylin. Magnified 200 diameters.)

As was observed by Baumgarten, who found the blood in the vessels between two ligatures still fluid after an interval of weeks, the mere stagnation of a mass of blood within a vessel is not sufficient to cause coagulation. The cause of the coagulation of blood that is not in circulation lies probably in part in the fact that certain portions of the mass of blood are no longer in contact with a living and inviolate vascular wall, which contact, according to Brücke, normally prevents coagulation. At the same time the production of a large amount of fibrin-ferment may provoke coagulation. This occurs, consequently, in vessels which have been ligated, when the endothelium is destroyed at the point of ligation. It takes place, furthermore, when, through the breaking up of large numbers of white blood-corpuscles, fibrin-ferment is set free in large quantity in the blood-vessels—a condition which may be experimentally produced by the injection of ruby-red blood (*lackfarbenes Blut*) whose cells are in part broken up.

The **fibrinous deposits from blood in circulation**, which not infrequently are formed on the internal surface of the heart or vessel-walls, are composed of masses either white, or of various shades of red, or with alternating red and white layers, and we may distinguish, accordingly, between **white, mixed,** and **laminated thrombi.** With the microscope we may discern that these thrombi are composed (Figs. 8 and 9) of granular and fibrous masses and of colorless and red corpuscles, which in varying proportions and arrangement make up their structure. The colorless thrombi consist almost exclusively of granular masses (Fig. 8, *a*) and of fibrogranular fibrin, the latter displaying at one point (*b*) a retiform arrangement of its fibres, while at another point (*c*) they run more nearly in a parallel direction. Both the granular masses and the fibres of fibrin contain only a scanty sprinkling of leucocytes. Other white thrombi contain more cells. In the mixed thrombi (Fig. 9), granular masses (*b*), more rarely hyaline masses, stringy fibrin (*c*), and red blood-corpuscles (*a*), in varying proportions and in diverse situations, compose the coagulated mass, and all of these component parts include more or less numerous—frequently very numerous—leucocytes (Fig. 9).

The fibrogranular masses which enter into the structure of the thrombi consist doubtless of fibrin which has been formed, just as takes place outside the vessels, by the action of a ferment. The granular and the hyaline masses, on the other hand, are at the present time regarded as structures formed from blood-plates which have become agglutinated together, although granular and hyaline masses may also be formed from leucocytes entangled in the meshes of the fibrin. The granular masses in the thrombi exhibit occasionally an arrangement similar to that of coral.

The formation of thrombi in circulating blood may be observed distinctly under the microscope, in suitable subjects, both in warm-blooded and in cold-blooded animals; and in this line it is more particularly the observations of Bizzozero, Eberth, Schimmelbusch, and Löwit which have led to very weighty conclusions.

When the blood flows through a vessel with its normal velocity, you may see under the microscope (Bizzozero, Eberth, and Schimmelbusch) a broad, homogeneous, red stream in the axis of the blood-vessel (Fig. 10, *a*), while at the sides lies a clear zone of blood-plasma free from red blood-corpuscles. This may be observed as well in the arteries as in the veins and in the larger capillaries, but is best seen in the veins; in the smaller capillaries, just large enough to permit the passage of the blood-corpuscles, this differentiation into an axial and a peripheral stream does not hold.

In the axial stream the different constituents of the blood are not recognizable; in the peripheral stream, however, isolated white blood-corpuscles appear from time to time (Fig. 10, *d*), and these may be seen to roll slowly on along the vessel-wall.

If the blood-current becomes retarded to about the degree which allows the observer to make out indistinctly the blood-corpuscles of the axial stream (Fig. 11, *a*), the number of white blood-corpuscles floating slowly along in the peripheral zone, and adhering also at times to the vessel-wall, becomes increased (Fig. 11, *d*), and they finally come to occupy this zone in considerable numbers.

If the current be still further retarded so that the red blood-corpuscles become clearly recognizable (Fig. 12, *a*), then, in the peripheral zone, alongside of the white blood-corpuscles appear blood-plates, which increase more and more in number with the progressive retardation of the flow, while the number of the leucocytes becomes again diminished. When total arrest of the blood-current finally occurs, a distinct separation of the corpuscular elements in the lumen of the vessel follows.

Fig. 10.

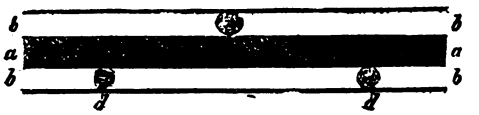

FIG. 10.—Quickly flowing blood-stream. *a*, Axial stream; *b*, Peripheral stream with isolated leucocytes, *d*. (After Eberth and Schimmelbusch.)

Fig. 11.

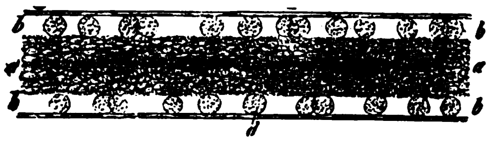

FIG. 11.—Somewhat retarded blood-stream. *a*, Axial stream; *b*, Peripheral zone with numerous leucocytes, *d*. (After Eberth and Schimmelbusch.)

Fig. 12.

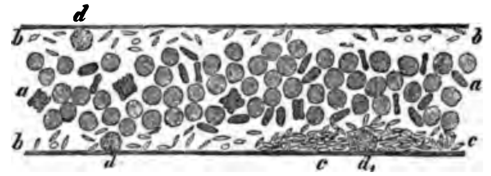

FIG. 12.—Greatly retarded blood-stream. *a*, Axial stream; *b*, Peripheral zone with blood-plates; *c*, A considerable collection of blood-plates; *d*, d_1, White blood-corpuscles. (After Eberth and Schimmelbusch.)

When, in a vessel in which the circulation is retarded, the intima is injured at a certain point by compression or by violence, or by chemical agents such as corrosive sublimate, nitrate of silver, or strong salt-solutions, and yet the lesion of the vessel-wall does not cause a complete arrest of the blood-current, we may observe (Bizzozero, Eberth, Schimmelbusch) *blood-plates adhering to the vessel-wall at the injured point*, and before long they cover the site of the injury in several layers. Frequently more or less numerous *leucocytes*, or *colorless blood-corpuscles*, become lodged in the mass (Bizzozero), and their number is proportionate to their abundance in the peripheral zone. Under some circumstances, indeed, the number of the leucocytes may be very considerable, and they may largely cover over the accumulation of blood-plates. In case of great irregularity of the circulation, or of extensive lesion of the vascular wall, *red blood-corpuscles* also may separate from the circulation, and *become adherent to the intima*, or to a layer of leucocytes previously deposited upon it. Not infrequently portions of the separated mass are swept away, in which case a new deposit of blood-plates is formed. Through a long-continued deposition of the elements of the blood the vessel may finally become completely closed.

Should a blood-vessel suffer a lesion, as above described, while the current of blood within it still remains swift, there is no adherence of blood-plates or of blood-corpuscles. When at any point blood-plates have become adherent in considerable numbers, they become, after a time, coarsely granular at the centre, and finally granular or homogeneous at the periphery, and become fused together into one compact mass. The final result of the process is the formation of a colorless *blood-plate thrombus*, within which more or less numerous *white blood-corpuscles* may be imprisoned. Eberth designates the sticking together of the blood-plates by the term *conglutination ;* their final fusion into a coherent thrombus he calls *viscous metamorphosis.*

If we compare the observations of Bizzozero, Eberth, and Schimmelbusch, as well as the recent observations of Löwit, on warm-blooded animals, with the histological findings in thrombi from the human subject, we are warranted in drawing the conclusion that the formation of thrombi in the circulating blood of man proceeds in a way similar to that observed in the lower animals, and we judge that their formation is directly dependent upon two causes: to wit, upon a *retardation of the blood-current* or other *disturbance of the circulation*—such as the *formation of eddies, which would direct the blood-plates against the vascular wall*—and upon *local changes in the wall of the vessel.* Probably, too, thrombosis is favored by *pathological changes in the blood.* From the variety of conditions under which thrombosis occurs in man we must assume, either that now one and again another of these causes plays the principal part in the formation of the thrombi, or that all three may concur equally in the process; and, on the other hand, that one of the causes alone is not ordinarily competent to cause thrombosis.

If a blood-plate thrombus or a conglutinate thrombus has formed at any point, coagulation may subsequently take place there, yielding threads of fibrin which imprison, in greater or less number—frequently in very great number—the cellular elements of the blood. *Conglutination and coagulation may accordingly occur together;* and the frequency with which this comes to pass, to judge from the composition of thrombi in man (Figs. 8 and 9), seems to denote that fibrin-ferment is set free in the formation of the blood-plate thrombus, and that hence, in the neighborhood of the conglutinated blood-plates, a process of coagulation occurs in the circumjacent peripheral zone of the blood-stream. If white blood-corpuscles alone are floating in the latter, the coagulating mass remains colorless (Fig. 8) and includes a greater or less number of leucocytes; while if red blood-corpuscles be circulating in the peripheral zone, or if the influence of the ferment extend as far as the axial stream, mixed thrombi will be formed (Fig. 9).

According to Eberth and Schimmelbusch, fibrin enters into the structure of artificially produced thrombi in those cases where thrombosis was provoked by the action of strong silver-solutions or by the introduction of foreign bodies.

Köhler, von Düring, and Hanau are of the opinion that the formation of many thrombi—as, for instance, those occurring in subjects who are in a condition of marasmus (Köhler, Hanau), or after traumatism (von Düring)—is to be ascribed to the toxic action of a ferment, and that local disturbances of the circulation merely determine the point of the coagulation. Vaquez is of the opinion that infection plays an important part in the formation of thrombi in cachectic subjects.

According to Naunyn, Franken, Köhler, Plosz, Gyorgyai, Hanau, and others, by the introduction of ruby-red blood (*lackfarbenes Blut*), of solutions of hæmoglobin, of the salts of gallic acid, of ether, and of other substances into the circulation, more or less extensive coagulation may be produced; nevertheless the results of the experiments are not constant (Schiffer, Hugyes, Landois, Eberth), and coagulation may not occur. The probability of effecting coagulation is proportionate to the degree of disturbance produced in the blood by the substance injected. A. Schmidt seeks the cause of coagulation after such injections in the fibrin-ferment. Eberth holds any such fermentation coagulation to be, at present, questionable, because it may likewise be produced (Edelberg) without fibrin-ferment, and because the solidified masses formed after such injections do not consist exclusively of fibrin, but also of "conglutinated blood-plates," of precipitated albuminoid bodies, and of disintegrated blood-corpuscles. Such injections, therefore, yield very diverse products, and consequently the experiments made in this manner possess only a limited value as a means of interpreting the mode of origin of thrombosis in the human subject.

According to Arthus and Pagès, blood, as it flows from a vein, becomes incapable of spontaneous coagulation when sodium oxalate, or sodium fluoride, or soaps are added to it in such quantities that the mixture comes to contain from 0.07 to 0.1 per cent. of the oxalate, or about 0.2 per cent. of the fluoride, or 0.5 per cent. of soap. These salts all operate by precipitating the calcium salts. If to blood, kept fluid by treatment with sodium oxalate, one tenth of its volume of a 1 per cent. solution of calcium chloride be added, coagulation takes place in from six to eight minutes, and the calcium salts enter into the constitution of the fibrin-molecule. The fibrin-ferment can act upon the fibrinogen only in the presence of calcium salts. Under the influence of the fibrin-ferment, and in the presence of calcium salts, the fibrinogen undergoes a chemical metamorphosis which results in the formation of a calcium-albumin compound—fibrin. For the occurrence of coagulation it is not necessary to invoke the aid of any peculiar fibrinoplastic, globulinoid substance, but there is need merely of the presence of calcium salts. The ferment which induces the coagulation is formed by the disintegration of cellular elements.

Bizzozero, some years ago, described as a new component of the blood certain minute, flat, homogeneous structures which he designated as blood-plates and regarded as identical with the hæmatoblasts described by Hayem. Relying upon profound experimental research, he concluded that it was these which, in breaking up, induced coagulation, while he declined to attribute this property to the white blood-corpuscles. Rauschenbach, Heyl, Weigert, Löwit, Eberth, Schimmelbusch, Hlava, Groth, and others have since then taken a stand against this doctrine of Bizzozero, as part of them deny any connection between the blood-plates and the coagulation of the blood, and part of them (Weigert, Hlava, Halla, and Löwit) do not regard the blood-plates as constant morphological elements of the blood, but rather as the débris of disintegrated white blood-corpuscles, or as the product of a precipitation of globulin (Löwit). From their contributions we may also gather that the destruction of white blood-corpuscles in a fluid containing fibrinogen may without doubt be followed by coagulation, thus showing that the blood-plates are at least not the only producers of fibrin. According to Groth, for example, the injection of large numbers of leucocytes into the circulation produces thrombosis. According to Rauschenbach, the dissolution of leucocytes is constantly occurring in the blood; but by an inhibitory action of the organism the supervention of coagulation is prevented, and the fibrin-ferment is either destroyed or rendered ineffectual.

In an essay published in the year 1875, Zahn first undertook a strict differentiation of the red from the white and the mixed thrombi, and showed that the first arose from coagulation of the blood, and the latter, on the other hand, from a deposit from blood in circulation. The colorless substance in the white and in the mixed thrombi, Zahn, basing his opinion on experimental research and on direct observation of the process of thrombosis in the blood-vessels of the frog, regarded as formations which were produced from white blood-corpuscles which had become separated from the blood-stream, then had become adherent to rough points on the vessel-wall, and finally had become fused together into a homogeneous or a granular mass. Up to a few years ago most authors coincided with these views, although since the investigations of Bizzozero, Lubnitzky, Eberth, Schimmelbusch, and Löwit there can be no doubt of the existence of the blood-plate thrombus also, into whose composition the white blood-corpuscles enter in but unimportant proportions. Eberth and Schimmelbusch do not look upon this process as a coagulation—a physical change which they, in common with Eichwald, regard as a precipitation or a crystallization—but as a process peculiar to itself, as a *conglutination* and *viscous metamorphosis* of the blood-plates. According to Eberth, the adhesion of the blood-plates to the vessel-wall follows only upon an irreparable alteration of the latter. The adhesion of the leucocytes is, on the other hand, a vital process.

According to Löwit, the blood-plates are not a constituent of normal blood, but rather make their appearance under definite conditions, and are nothing more than globulin precipitated in the form of plates. For their appearance very slight alterations in the circulation or in the composition of the blood suffice, and it is therefore difficult to make observations upon blood in circulation without causing them to appear; it is nevertheless possible, with proper precautions in investigating, to prove that the blood circulating through the mesentery of the mouse contains no morphological elements beyond the red and the white blood-corpuscles. Alterations of the vessel-wall and retardation of the blood-current lead to the separation of blood-plates and their adhesion to the walls of the vessel; and the blood-plates so separated then quickly undergo metamorphosis into a substance closely resembling ordinary fibrin, become comparatively insoluble, swell up, and take on a partly granular appearance. The fibrin derived from the blood-plates is very like ordinary fibrin in its capacity for taking dyes, and the formation of a blood-plate thrombus is also, indeed, a kind of coagulation. In cold-blooded animals no blood-plates appear under the conditions which would cause them to be formed in warm-blooded animals, but globulin is precipitated in a granular condition. Certain minute fusiform elements contained in the blood of birds and of cold-blooded animals, which Bizzozero, Eberth, and Schimmelbusch hold to be the equivalents of the blood-plates, are none other than colorless cells which develop, part into leucocytes and part into red blood-corpuscles. They accordingly are provided with a nucleus and may assume a spherical form, whereas the blood-plates are without a nucleus and are subject only to passive changes of form. Alterations of the vascular walls and retardation of the blood-current in cold-blooded animals lead to the formation of thrombi consisting essentially of leucocytes and capable of transformation into granular masses. At the beginning of cell-deposition we find the spindle-shaped leucocytes deposited with especial frequency.

According to observations made by Wlassow, in my laboratory, I feel myself justified in adopting the opinion that *the blood-plates are a product of the red blood-corpuscles*, and either are thrown off from the bodies of degenerating red blood-corpuscles, or are formed on the disintegration of the same. Wlassow studied both the early stages of thrombus-formation and also the behavior of the blood-corpuscles when treated with various fluids, and his observations indicate, on the one hand, that at the beginning of a thrombosis in circulating blood red blood-corpuscles do become adherent to the vessel-wall and may subsequently become changed and transformed into a granular mass, and, on the other hand, that a portion of the red blood-corpuscles—presumably those which are the oldest and are approaching their decadence—are extremely unstable cells, out of which structures with properties corresponding to those of the blood-plates are readily formed. As to whether such structures are developed under normal conditions, or whether, in the normal breaking down of the red blood-corpuscles, the colorless components of their structure enter immediately into solution, could not be decided; this much only could be demonstrated: that the most diverse influences caused a plasmoschisis (a splitting up of the blood-plasma), accompanied by a formation of the so-called blood-plates.

A. Schmidt, in his work on the blood, published in 1892, wherein he collects the results of many years of study on coagulation, regards the fibrin-ferment or *thrombin* as a derivative of the life of the cells, which is developed from an inactive earlier state, *prothrombin*, under the influence of certain *zymoplastic substances*. In the same way he regards the *fibrinogenous substance*, or *metaglobulin*, as a product of the disintegration of cellular protoplasm. If this view be correct, and if the investigations of Wlassow find further corroboration, then the generators of coagulation, as well as those of thrombosis, must all be regarded as cellular derivatives, and it would then be particularly *the red blood-corpuscles which would be the source of the materials of coagulation.*

According to Corin, *coagulation occurs in the blood after death only when the blood already contained ferment during life;* and the extent of the coagulation is directly proportional to the amount of ferment present at the time of death. A further production of ferment does not occur after death; on the contrary, the vessel-walls probably constitute a body inhibiting coagulation. Between the blood of those who have died suddenly (cases of strangulation) and that of those who have died more slowly, the difference is only relative, depending upon the amount of ferment present. No value can therefore be ascribed to the fluidity of the blood in the diagnosis of the mode of death.

§ 40. **Thrombosis** occurs most frequently in cases of degeneration and inflammation of the intima of the heart and of the vessels, as well as under certain circumstances which, like compression, stricture, or dilatation of the vessels, fatty infiltration and fatty degeneration of the heart, stenosis and insufficiency of the valvular orifices, etc., cause a retardation or an arrest of the circulation. If thrombi occur in cachectic individuals, they are called **marasmic thrombi** (thrombi marantici). When **perforating wounds of vessels** are not too large, they become closed by blood-plates and white blood-corpuscles which adhere to the edges of the opening and are also deposited all about it, so that in the wound there is formed a white thrombus projecting into the lumen of the vessel.

Different varieties of thrombi are distinguished according to their re-

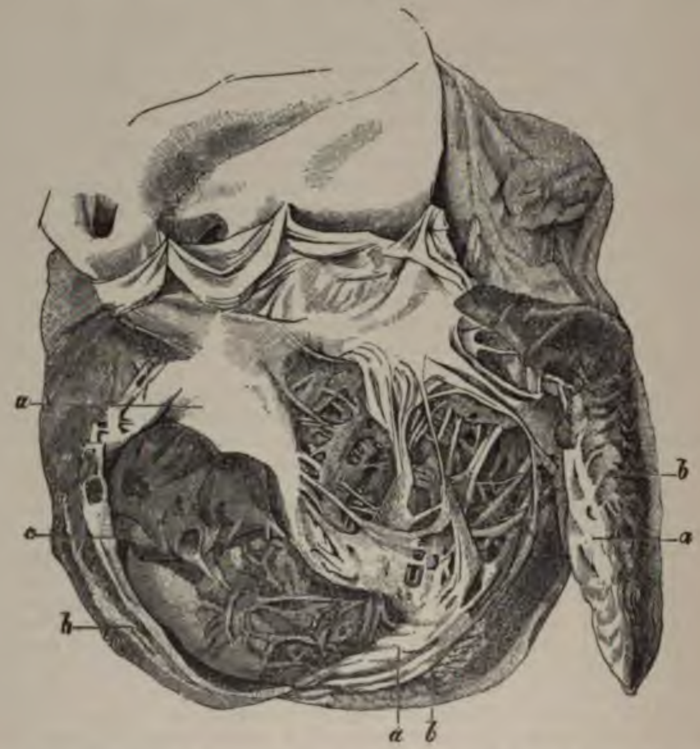

FIG. 13.—Thrombus-formation in the heart as a result of inflammatory degeneration and aneurismal dilatation of the heart-wall. *a*, Inflammatory thickening of the endocardium; *b*, Inflammatory degeneration of the myocardium; *c*, Thrombus. (Two-thirds natural size.)

lations to the vessel containing them. Thus a **parietal thrombus** is one attached to the wall of the heart (Fig. 13, *c*) or of a vessel; a **valvular thrombus,** one which is situated upon a valve of the heart or of a vein (Fig. 14, *d*). Either kind may consist only of delicate, transparent, almost membranous and hyaline deposits; and then, again, they are often thicker and tougher, and project into the lumen of the heart or blood-vessel, as the case may be. Their surface, in the latter case, often shows rib-like ridges of paler appearance than the other parts. If the lumen of a vessel becomes closed by a thrombus, the latter is spoken of as an **obturating thrombus** (Fig. 14, *a*, *b*). The coagula first formed are designated as **primary** or **autochthonous;** those subsequently deposited upon these, as **induced thrombi.** Through growth by accretion a parietal thrombus may become obturating. In such a case it not infrequently happens that a red thrombus is superadded to one originally white or mixed in color (Fig. 14, *c*), inasmuch as the thrombosis began in circulating blood, while later, after the closing off of the vessel, the blood became stagnant and the whole mass then coagulated. The opposite occurs when a red thrombus, obturating a vessel, contracts down to a smaller volume, and thus leaves a channel once more for the passage of the blood.

Thrombi may occur in all parts of the vascular system. In the *heart* it is particularly in the auricular appendages and in the recesses between the trabeculæ carneæ, as well as on any diseased spot of the heart-wall (Fig. 13, *c*), that they establish themselves. Their formation starts in the deep intertrabecular recesses; but through continual accretions more considerable coagulation-masses are formed, which project in the form of polypi above the general surface, and therefore are known as **heart-polypi.** They are sometimes more or less spherical in shape, with a broad base, and again they are more pear-shaped; their surface is often ribbed. As a rare occurrence, large globular or pear-shaped thrombi may become loosened, and then, in case they cannot pass the ostium, they lie free in that chamber of the heart (most frequently an auricle) in which they had their origin. **Free globular thrombi** are sometimes seen in the auricles in cases of stenosis of the auriculo-ventricular orifices, although they are very rare. Very probably they become increased in

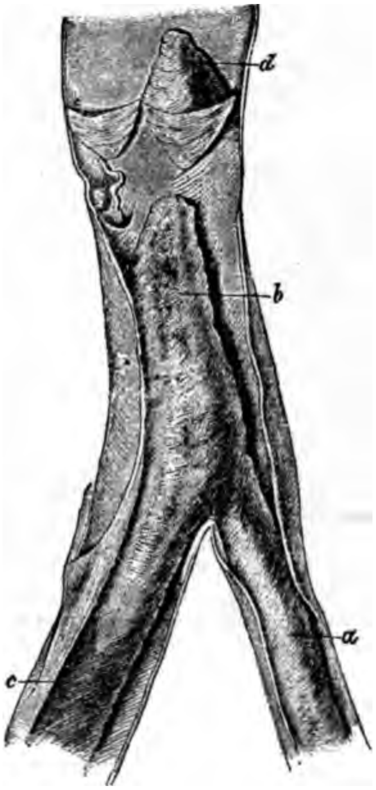

FIG. 14.—Thrombosis of the femoral and of the saphenous vein. *a*, *b*, An obturating thrombus, of mixed coloring and laminated; *c*, Red thrombus with peripheral attachment; *d*, Thrombus protruding from a valve. (Reduced one fourth.)

size by the deposition of fresh layers of fibrin after they have been set loose. If coagulated masses attach themselves to an inflamed valve, they are designated as **valvular polypi.** Parietal and valvular polypi may become very bulky and may fill up a large part of one of the heart-chambers.

In the arterial trunks thrombi are found in a great variety of places, and are particularly apt to occur behind constrictions and in dilatations. Occasionally, in cachectic individuals with a much-degenerated intima, parietal thrombi, white, or of a mixed color, and superficially adherent, are formed in the aorta. In the veins thrombi occasionally are formed in the pockets of the valves (Fig. 14, *d*), from which they gradually protrude and develop into obturating thrombi. Frequently a thrombus grows out from a lesser vein in which it was formed into the lumen of a larger vein. So, for instance, a thrombus having its origin in one of the lesser veins of the lower extremity may grow up through the vena cava inferior until it reaches the heart.

Thrombi of the smallest vessels arise most frequently in consequence of disease of the surrounding tissues, and especially after infections and toxic inflammations and necrotic processes, and they have, for the most part, a hyaline composition, though by proper technique (Weigert's fibrin-stain) it may often be demonstrated that they are made up of stringy fibrin and blood-plates. They are found, furthermore, after superficial burns (Klebs, Welti, Silbermann) and after poisoning—for instance, poisoning with corrosive sublimate (Kaufmann)—especially in the lungs. They frequently exist in hæmorrhagic infarcts (Fig. 6, *c*) which are already of a certain age. Thrombi, too, originating in the capillaries, may develop in the efferent veins, partly for the reason that through the obturation of a great number of capillaries the blood flows slowly into the veins, and partly, also, for the reason that disintegrating blood-corpuscles and blood-plates find their way to the veins in great numbers. As a matter of course, impermeability of the capillaries and constriction of the arteries, due to any other causes, produce thrombi in the first of these two ways.

§ 41. The first deposits in the formation of a thrombus are delicate, transparent, or whitish layers. The fully formed thrombus is a compact, dry mass, firmly attached to the inner surface of a vessel or of the heart, with the different qualities of color and structure described above. Thrombi, originally soft and succulent, undergo in time a process of **contraction,** and thereby become firmer and more dry. In this way, in case of obturating thrombi, an obliterated channel may become open once more for the passage of the blood.

With long-continued contraction, the fibrin, the blood-plates, and the blood-corpuscles may become converted into a tough mass, which long remains in this condition, grows fast to the vessel-wall, and eventually becomes **calcified.** This occurs both in valvular thrombi and in those located in the vessels. Chalky concretions in the veins, known as **phleboliths,** are formed in this way. Similar formations in the arteries, which occur, however, less frequently, we may call **arterioliths.**

Shrinking and calcification constitute a comparatively favorable issue of thrombosis. Far less favorable are the various kinds of disintegration which frequently follow and are known as simple and as puriform or septic yellow softening. In the **simple softening** the central portion of the thrombi becomes converted into a grayish-red, gray, or grayish-white grumous mass, consisting of broken-down and shrunken red blood-corpuscles, pigment granules, and colorless granular débris. If the softening extends to the superficial layers, and if there is, at the same time, a certain strength of blood-current in the region of the thrombus, the softening débris are swept along into the circulation. This occurs both with heart-polypi and with venous thrombi, especially when the tip of a thrombus in a small vein projects into the lumen of a larger vein through which the blood still flows freely. A frequent result of such softening is the formation of emboli (cf. Fig. 2, page 41).

In the **yellow puriform** or **septic softening** the thrombus breaks down into a yellow or grayish-yellow or reddish-yellow mass similar to pus, grumous, creamy, and foul-smelling, which along with pus-corpuscles contains a great deal of a finely granular substance made up of fatty and albuminous detritus and micrococci. This mass acts as a destructive irritant, causing inflammation by its contact. As a result the intima becomes cloudy, and a suppurative inflammation arises in the media and adventitia, as well as in the parts about the vessel. After a short time all the vascular tunics become infiltrated and present a dirty-yellow or grayish-yellow appearance. Ulcerative destruction of the tissues eventually supervenes. If the puriform masses are carried along by the blood-current to other places, there too they lead to necrosis and septic disintegration of the tissues, and to suppurative inflammation, which affects not only the wall of the vessels, but also the circumjacent tissues.

The process of puriform softening of a venous or an arterial plug, coupled with the infiltration of the vascular wall, is denominated **thrombo-phlebitis purulenta** or **thrombo-arteritis purulenta.** The inflammation of the vessel-wall may start either in the softening thrombus or else in the parts adjacent to the vessel. In the latter case the softening of the thrombus either goes on simultaneously with the inflammation of the vessel-wall or else succeeds it. These occurrences take place most frequently in the neighborhood of purulent foci.

The most favorable issue of thrombosis is in the **organization of the thrombus**—that is, in its being **replaced by vascularized connective tissue.**

The new connective tissue is developed from proliferating endothelial cells; but if these have been destroyed, then plastic migratory cells arrive from the outer layers of the vessel-wall. The thrombus itself takes no part in the process of organization; it is a lifeless mass exciting inflammation in surrounding parts. In course of time the thrombotic mass becomes absorbed, and its place is taken by vascularized connective tissue (Fig. 16, *g*).

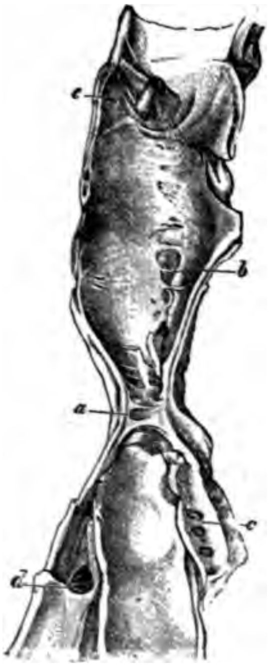

FIG. 15.—Remains of a thrombus of the right femoral vein, formed three years before death. *a*, Obliterated portion of the vein (the right common iliac vein was likewise obliterated): *b*, *c*, *d*, Bridles of connective tissue in the interior of the vein and of its branches; *e*, Recent thrombus. (Natural size.)

The cicatricial tissue occupying the place of the thrombus shrinks more or less in course of time. Cicatrices after ligation become, in this way, very small. Such a cicatrix in the continuity of a vessel may later have the appearance of merely a thickening of the wall of the vessel, or there may remain only threads and trabeculæ (Fig. 15, *b*, *c*, *d*), which cross the lumen of the thrombosed vessel, so that the blood-current can once more pass the affected spot without serious impediment. It not infrequently happens, nevertheless, that the connective-tissue bridles crossing the lumen of the vessel cause a marked lessening of its calibre; and this may proceed to a complete obliteration of the vessel, so that the blood-

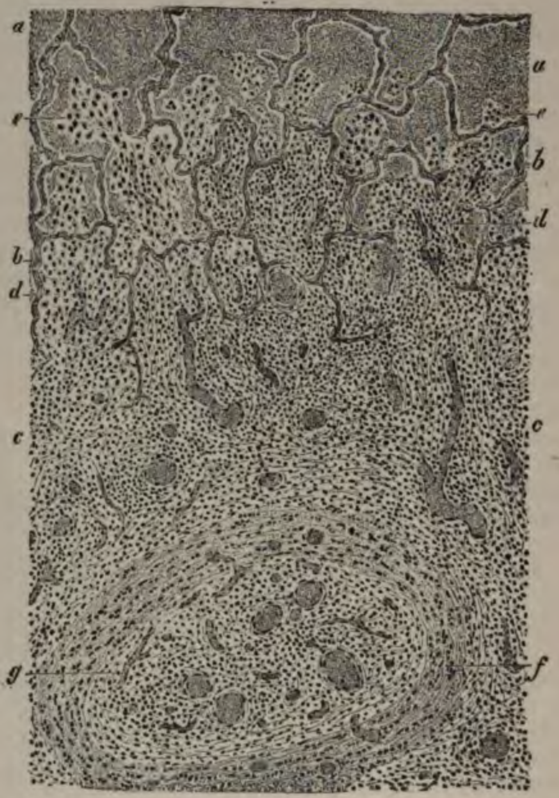

FIG. 16.—Portion of the edge of a pulmonary infarct with obliteration of the artery in the process of healing. *a*, Extravasated blood changed into yellowish granular masses; *b*, Necrotic interalveolar septa without nuclei; *c*, Newly formed connective tissue; *d*, vascular granulation tissue within the alveoli; *f*, An artery; *g*, Vascularized connective tissue occupying the place of an embolus in the artery. (Specimen hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 45 diameters.)*

* Near the top of the cut, right and left, are structures marked *e*. No description of them is given in the original. They appear to represent newly formed vascular loops with nucleated endothelium, pushing their way into the granular masses, *a*, *a*.—TRANSLATOR'S NOTE.

vessels for a greater or less distance become converted entirely into solid fibrous cords.

Pieces broken off from a thrombus and carried into an artery and there wedged—so-called **emboli**—generally induce fresh deposits of fibrin upon their surface (Fig. 2, *c*, page 41). Afterward they undergo the same changes as thrombi, and may either soften and break down or become shrunken (Fig. 17, *a*) and calcified. If the emboli are non-infectious they generally become replaced by vascular connective tissue (Fig. 16, *g*).

In many cases this new formation of connective tissue leads to the obliteration of the artery (Fig. 16, *f*, *g*). In other cases in the place of the embolus there becomes developed only a ridge of connective tissue or perhaps a knobbed or a flattened thickening of the intima. In still other cases the lumen of the vessel is traversed by

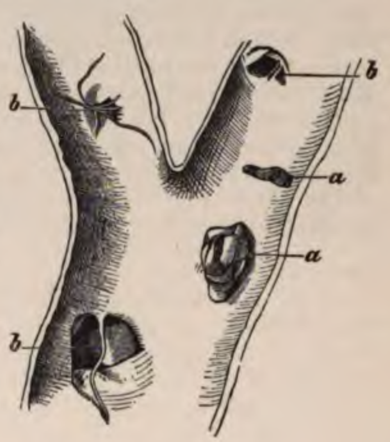

FIG. 17.—Remains of an embolic plug of a branch of the pulmonary artery. *a*, Shrunken embolus traversed by threads of connective tissue; *b*, Bridles of connective tissue crossing over the orifices of branch vessels. (Natural size.)

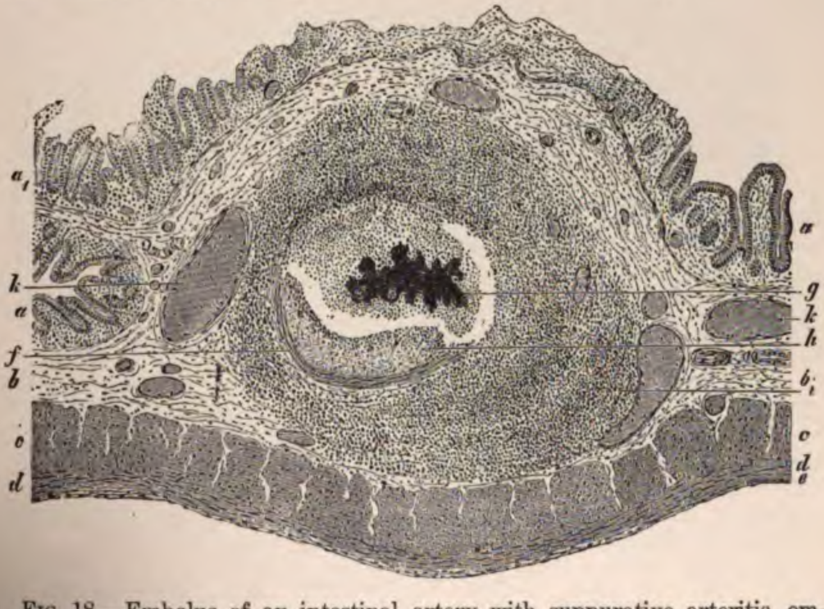

FIG. 18.—Embolus of an intestinal artery with suppurative arteritis, embolic aneurism, and periarteritic metastatic abscess. *a*, *b*, *c*, *d*, *e*, Layers of the in-inal wall; *f*, Wall of the artery; *g*, The embolus, surrounded with pus-corpus-ing within the dilated and partially suppurating artery; *h*, Parietal : *i*, Periarterial purulent infiltration of the submucosa; *k*, Veins gorged (Specimen hardened in alcohol, stained with fuchsin, and mounted alsam. Magnified 30 diameters.)

bridles of connective tissue (Fig. 17, *b*), which either run separately, or, through mutual interlacings, form a wide- or a close-meshed network.

If the emboli contain pyogenic organisms, which is especially apt to be the case if the emboli come from a thrombus lying in a suppurating focus, suppuration then arises at the site of the embolus (Fig. 18, *g*), and occasionally ulceration also.

§ 42. In those conditions which have been described above as active and passive hyperæmia respectively, the blood during life is in circulation. In the active, congestive form the velocity of the blood-current is increased; in the passive form—venous hyperæmia—it is diminished. If the passive form become very marked, so that the blood entering a part cannot find exit, the circulation in the small veins and capillaries, and even in the smaller afferent arteries, may come to a complete standstill; and that condition then obtains which is known as **stasis** or **stagnation of the blood** (Fig. 19). Inasmuch as fresh masses of blood from the arteries strive with each pulse-beat to force their way into the area of stag-

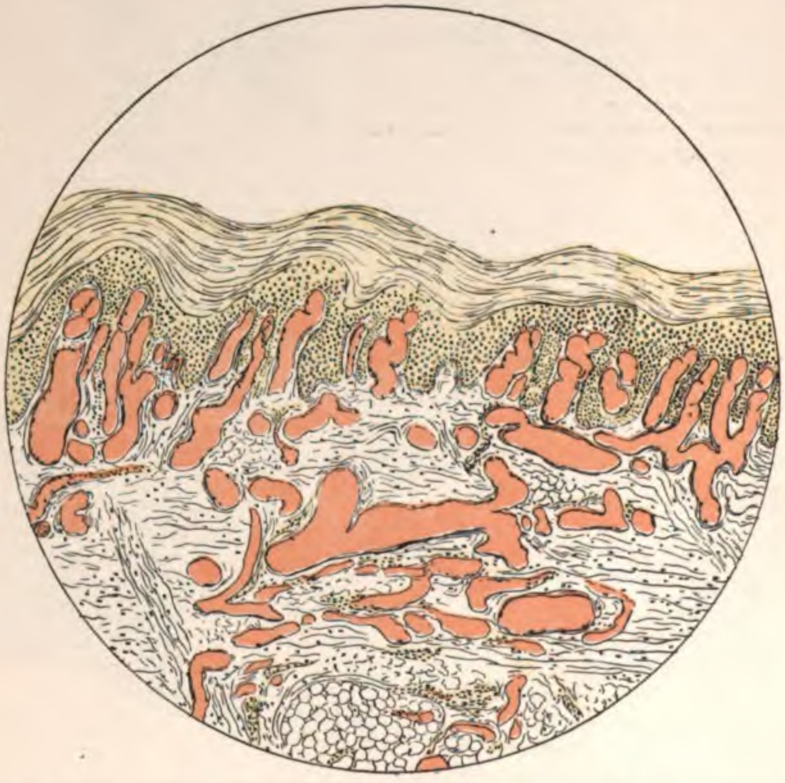

FIG. 19.—Stasis from venous hyperæmia in the vessels of the corium and of the papillæ of the plantar surface of the toes in a man succumbing to valvular disease, heart-failure, and arteriosclerosis. Deep-violet coloring and commencing gangrene of the toes. (Specimen hardened in Müller's fluid, stained with alum carmine, and mounted in Canada balsam. Magnified 20 diameters.)

nation, and thus distend the capillaries and the veins more and more, the pressure within these rises to be the same as that at the point of divergence of the nearest permeable artery (von Recklinghausen), and by this means a great portion of the fluids of the blood is pressed out of the capillaries and the veins. The red blood-corpuscles consequently become so closely jammed together that their contours are no longer discernible, and the total contents of the vessels form a homogeneous, scarlet-red column (Fig. 19). At the same time, however, the blood-corpuscles are not fused together. As soon as the obstacle to the outflow is done away with and circulation is once more resumed, the individual blood-corpuscles become once more separated from one another.

Stasis is produced not only by damming back of the blood, but also by numerous influences affecting the vessel-walls and the blood itself. Thus *heat* and *cold*, *irritation with acids or with alkalis*, the *action of concentrated-sugar or common-salt solutions*, *of chloroform*, *alcohol*, etc., may cause not only contraction or relaxation of the vessels and disturbances of the circulation, but may, under certain circumstances, produce stasis. According to von Recklinghausen, these agents accomplish their untoward results chiefly in abstracting water from the blood and from the vessel-wall. Possibly the composition of the blood-corpuscles and of the blood-plasma becomes, furthermore, so altered that the blood-corpuscles become less mobile (von Recklinghausen). The stasis which occurs in tissues which are taken from the interior of the body and exposed to the air is to be ascribed to *evaporation*. Through the operation of heat and cold, it is highly probable that changes occur not only in the vessel-wall, but also in the constitution of the blood. Many chemical agents so damage the vessel-walls that the frictional equation becomes greater, while at the same time the wall itself becomes more pervious.

IV. Œdema and Dropsy.

§ 43. The unconfined fluid which permeates the tissues is essentially a transudation from the blood, though, under some circumstances, a portion of the juice contained in the cells and fibres may also pass over into the unconfined fluid of the tissues (Heidenhain). The exudation of fluid from the vessels is not a process of simple filtration, but is rather to be regarded as a process of secretion (Heidenhain) effected by means of the specific function of the capillary walls. The fluid secreted from the capillaries, which becomes mingled with the products of tissue-metabolism, is absorbed by the lymphatics from the interstices of the tissues, and is returned to the veins through the ductus thoracicus.

Every increase in the transudation of the blood-fluids occasions primarily an increase in the permeation of the tissues, which, for the most part, is again reduced by an increased absorption through the lymphatics. This equilibration, however, has its limits; with increased transudation from the blood-vessels we get a more or less permanent oversaturation of the tissues with the transuded fluid.

That condition which is produced by this collection of fluid in the tissues is known as **œdema** or as **dropsy**, and we distinguish between a general and a limited dropsy according to the extent of the affection. Œdema extending over superficial portions of the body is known as **anasarca** or as **hyposarca**.

That portion of the blood which is transuded from the vessels is always considerably less rich in albumin than the blood-plasma. The fluid collects first in the interstices of the tissues as free tissue-fluid, and may then soak into the tissues themselves and thus cause swelling of the cells and of the fibres, and, under some circumstances, the formation of vacuoles (Fig. 20), due to the accumulation of drops of fluid within the cells or their derivatives.

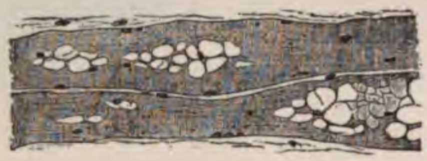

FIG. 20.—Longitudinal section through the œdematous muscle-fibres of the gastrocnemius of a subject with chronic œdema of the legs. (Specimen hardened in Flemming's acid-mixture, stained with safranine, and mounted in Canada balsam. Magnified 45 diameters.)

This may be most frequently demonstrated in tegumentary and in glandular epithelium, but becomes evident also in other tissue-elements, particularly in muscle-fibres (Fig. 20), whose fibrillæ become separated by drops of fluid. It may happen, moreover, that cells in œdematous tissues, particularly in the lungs and the serous membranes, become loosened from their attachment, and the fluid comes to contain an admixture of epithelial and endothelial cells in considerable numbers.

Tissues which are the seat of œdema appear swollen, though the degree of swelling is essentially dependent upon the structure of the tissue. The skin and the subcutaneous cellular tissue are able to take up into the interstices of their structure large quantities of liquid, and an extremity may accordingly become enormously swollen with œdema. Its appearance is then pale, it has a doughy feeling, and upon pressure with the finger an indentation remains behind. An incision sets free an abundance of clear liquid and reveals the tissues thoroughly saturated with fluid.

The lung behaves in a similar way. Owing to its limited room it is not especially distensible, but it contains multitudes of cavities filled with air, and these, upon the advent of œdema, become filled with liquid, which, on pressure, escapes from a cut surface, mingled with air-bubbles.

Far less capable of retaining fluids is the kidney; consequently but little fluid flows off on section of an œdematous kidney, though the cut surface is moist and glistening.

The amount of blood contained in œdematous tissues is variable, and their color is consequently so also.

Such cavities of the body as are the seat of dropsical effusion contain at one time a considerable, and at another a very small amount of clear, generally light-yellow, rarely quite colorless, alkaline fluid, which occasionally contains a few flakes of fibrin (cf. the section on Inflammation). Compressible organs are compressed by the exudation, and cavities are dilated.

A collection of fluid in the abdominal cavity goes by the name of **ascites.**

The proportion of albumin in pure transudates is not the same in all the tissues and cavities of the body, but differs within wide limits. According to Reuss, the proportion of albumin in transudates of the pleura is 22.5 *pro mille;* of the pericardium, 18.3; of the peritoneum, 11.1; of the subcutaneous cellular tissue, 5.8; of the cerebral and spinal cavities, 1.4. Therein lies a proof of the differing constitution of the vessel-wall in the several tissues of the body.

The water of the various organs and tissues, according to Heidenhain,* is made up of three parts—of the water present in the blood, of the lymph of the organ under consideration, and of the water contained in the cells and in the fibres—the tissue-fluid proper. This tissue-fluid may, under certain circumstances, undergo considerable variations, increasing at the expense of the watery part of the blood or of the lymph, or diminishing as the latter increases.

If the proportion of crystalloids in the blood (urea, sugar, salts) become greater, both blood and lymph come to contain a greater proportion of water, which is possible only in this way: that these substances, when thrown into the blood, pass over into the lymph-spaces, and, by their affinity for the tissue-fluids, excite a discharge of water from the tissue-elements. The prompt passage of the crystalloids between the blood and the lymph is accomplished with the aid of a force inherent in the capillary cells; that is, it is not a phenomenon of mere diffusion. The evidence of this lies in the fact that the proportion of salts or of sugar in the lymph is oftentimes greater than that in the blood.

§ 44. According to the etiology we distinguish four varieties of œdema—namely, the *œdema of stagnation, inflammatory œdema, hydræmic œdema*, and the *œdema ex vacuo*.

The **œdema of stagnation** is the result of a partial stagnation of the blood-circulation. If in any manner the outflow of venous blood be impeded, if the obstacles impeding the blood-flow exceed a certain limit, the fluids of the blood then seek a lateral outlet and escape from the vessels. The amount of the escaping fluids increases in proportion to the degree of discrepancy between the inflow and the outflow of the blood, and is therefore increased by an increase in the afflux of blood.

The escaping fluid never contains much albumin, though with increase of pressure in the veins the proportion of albumin rises (Senator); the fluid, furthermore, contains more or less numerous red blood-corpuscles, and their number increases with the degree of obstruction.

The immediate result of an increased transudation is an increased flow of lymph, and this may suffice to carry off all the fluid. If it do not so suffice, the fluid collects in the tissues and we have a condition of œdema or dropsy. According to Landerer, the occurrence of this condition is favored by the fact that the elasticity of the tissues becomes diminished in consequence of the long-continued increase of the pressure to which they are subjected.

Obstruction to the flow of the lymph, as experiments in this line have shown, is not ordinarily succeeded by œdema. In the first place, the lymph-vessels in the various parts of the body have elaborate anastomoses, so that an obstruction to the flow of lymph does not readily occur; and even when all the efferent lymphatics of an extremity are closed off, provided the lymph-formation remains normal, no dropsy generally ensues, inasmuch as the blood-vessels themselves are able to take up the lymph again. Only the *occlusion of the ductus thoracicus* is ordinarily followed by stasis of the lymph and by œdema, particularly by ascites; but we must still observe that even in this case collateral channels may open up, and may suffice to carry off the lymph.

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* "Versuche und Fragen zur Lehre von der Lymphbildung" [Essays and Queries Regarding the Theory of Lymph-formation], *Arch. f. d. ges. Physiologie*, 49. Bd., 1891, and *Verh. des X. internat. med. Cong.*, ii., Berlin, 1891.

Although lymphatic obstruction is not ordinarily sufficient to cause œdema of itself, yet it does increase an œdema already produced by excessive transudation from the blood-vessels.

The amount and the character of the fluid which escapes from the capillaries and the veins are not dependent merely upon the intravascular pressure and the degree of obstruction to the blood-current, but also upon *the constitution of the vessel-wall.* Therefore not only disturbances of the circulation, but also *changes in the vessel-wall,* and in the endothelium in particular, may lead to an increase or to a diminution of the transudation. Indeed, as the outcome merely of long-continued obstruction and the resulting imperfect renewal of the blood, but still more in consequence of chronic *ischæmia,* of *imperfect oxygenation* or of *chemical changes in the blood,* or by reason of the *effect of high or low temperatures* or of *traumatic lesions,* etc., the walls of the vessels may become more pervious to the fluid as well as to the corpuscular elements of the blood. Just what changes the vessels suffer under these circumstances we are not able to state precisely, but it is proper enough to suppose that injury to the endothelial cells and to the cementing substance between them is the most important part of the lesion. If through these influences œdema arise, then we may distinguish, according to the cause, **toxic, infectious, thermal, traumatic, ischæmic œdema,** etc., and such a division would have much to commend it. Hitherto the kinds of œdema here under consideration have generally been relegated to two groups, inflammatory œdema and cachectic œdema.

Inflammatory œdema is most undoubtedly to be referred to an *alteration in the wall of the vessel,* and is seen both as an independent affection, in the shape of circumscribed or more extensive swellings and dropsical effusions, and also as an epiphenomenon in the neighborhood of severe inflammatory processes. In the latter case it is frequently called *collateral œdema.* Inflammatory œdema is differentiated from the œdema of stagnation in that the transuded fluid holds far more albumin in solution and is much richer in white blood-corpuscles, and, furthermore, in that considerable coagula occur in it (cf. the section on Inflammation). Its origin is to be sought sometimes in infectious and toxic, sometimes in thermal or traumatic influences, and again in a temporary ischæmia.

As to **hydræmic** or **cachectic œdema,** it was long thought that hydræmia proper—i.e., diminution of the solids of the blood—as well as hydræmic plethora—i.e., retention of water in the blood—could be an immediate cause of increased transudation from the blood-vessels. It was supposed that the vessel-walls behaved as animal membranes and allowed a fluid poor in albumin to pass through more readily than one containing a larger amount of albumin. The vessel-walls are not, however, lifeless animal membranes, but are to be regarded as a living organ. Hydræmia, experimentally produced, is not, according to Cohnheim, followed by œdema; and even when we succeed, through the production of hydræmic plethora—i.e., through overfilling the vascular system with watered blood—in obtaining an increased transudation from the vessels, and eventually œdema, this œdema supervenes only after the proportion of water in the blood has become very large, and, moreover, it does not develop in the same localities where the so-called hydræmic œdema in man develops. We are driven, then, to assume that the œdema of cachectic individuals, as well as that of "nephritics"—i.e., of individuals whose renal function is imperfect—is due essentially to an *alteration of the vessel-*

walls, an alteration caused either by the hydrated condition of the blood or by a poison circulating in that fluid. Probably other lesions of the tissues should be considered in this connection (Landerer)—lesions which diminish the elasticity of the tissues. Under these conditions the *hydræmia indeed favors the appearance of œdema*, but is not the sole cause thereof, nor does it determine the site of the same.

Hydræmic œdema is distinguished from inflammatory œdema by the facts that the transudate is less rich in albumin, and that it contains corpuscular elements in smaller proportion.

Œdema ex vacuo occurs principally in the cranial cavity and in the spinal canal, and arises in all cases where a portion of the brain or of the spinal cord is lost and its place is not taken by some other tissue. In atrophy of the brain and of the cord the subarachnoidal spaces in particular become enlarged; occasionally the ventricles also. Local defects either become filled by dilatation of the nearest subarachnoidal spaces or of the adjacent portions of the ventricles, or fluid collects directly at the site of the defect.

According to Cohnheim and Lichtheim, injection of aqueous solutions of salt into the vascular system of dogs *—hydration of the blood—does not produce œdema. If the mass of the blood is increased, an increase is observed in almost all the secretions (saliva, intestinal juices, bile, urine, etc.) and also in the flow of lymph; the last, however, not universally—for instance, not in the extremities. In an advanced state of hydræmic plethora the abdominal organs become œdematous, but never the extremities. Control-experiments recently made by Francotte confirm the observation that hydræmic plethora artificially induced in the lower animals results directly in dropsy of the abdominal organs; but Francotte obtained œdema also of the skin and of the subcutaneous cellular tissue.

The view that the so-called hydræmic œdema is merely the result of an increase of the absolute amount of water in the blood is championed especially by von Recklinghausen and recently by Pisenti also. The distribution of the dropsy is, according to von Recklinghausen, essentially dependent upon bodily position, external pressure, obstructions to circulation, difference in innervation of the several vascular areas, and upon the consequent difference in the fulness of their vessels.

I can subscribe to these opinions only in so far as they apply to the modifying factors named, not, however, as regards their general drift. Opposed to this are not only the experiments of Cohnheim above referred to, but also the fact that in nephritic as well as in cachectic subjects œdema not infrequently appears at a time when no hydræmic plethora is present, and the further fact that, with hydræmic plethora, œdema may be wanting. I therefore look upon the increase in the amount of water as only one factor which is favorable to the occurrence of œdema.

According to Löwit, for the development of an œdema of stagnation in the lungs, an obstruction to the outflow of the blood from the lungs is not alone sufficient; there must at the same time be an increased afflux of blood to the lungs, which, moreover, must persist for a certain length of time.

According to Heidenhain, the specific function of the capillary walls plays a controlling part in the formation of lymph, and consequently the formation of this material can be influenced by various substances present in the blood. The fact that crystalloid substances are quickly eliminated from the capillaries and cause a discharge of tissue-fluids into the lymph has already been mentioned in § 43. Heidenhain has, however, found substances which, when injected, increase the transudation of water from the blood-vessels into the lymph. This may be accomplished, for instance, with decoctions of the muscles of crabs and of fresh-water mussels, or of the heads and bodies of leeches, or with injections of peptone and of egg-albumin; and by these means the quantity of lymph flowing from the ductus thoracicus may be increased from five to six fold. There is also a concomitant increase in the proportion of organic matter in the lymph. The exciting substance must then stimulate the function of those cells in the capillary walls which secrete the lymph. If we reason from these observations, it seems very probable that many skin-affections described as neuropathic, and characterized by cutaneous hyperæmia accompanied by œdematous swelling—as, for example, urticaria, erythema nodosum, and herpes zoster—are to be regarded as intoxications coupled with nervous affections and with disturbances of the secretory activity of the capillaries. Possibly the secretion of the capillaries may be affected also by direct innervation.

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* *Virch. Arch.*, 69. Bd.

V. Hæmorrhage and the Formation of Infarcts.

§ 45. By **hæmorrhage** we understand the escape of all the ingredients of the blood from the vessels (*extravasation*) into the tissues or upon a free surface. It is either *arterial* or *venous* or *capillary*, or else occurs from all the vessels at once. The blood which has escaped from the capillaries is termed an **extravasate**; at the same time, for the various forms of hæmorrhage there are a great variety of names in use. If the hæmorrhagic foci are small and form more or less sharply defined, punctate, red or reddish-black spots, we designate them as *petechiæ* or *ecchymoses*; if they are larger and less clearly defined, as *suggillations* and as *bloody suffusions*. If the affected tissue is solidly infiltrated with the escaped blood, but yet not rent nor broken up, we call it a *hæmorrhagic infarct*. If the blood forms a tumor we speak of it as a *hæmatoma*, or a *blood-tumor*.

Considerable hæmorrhages are always coupled with a pronounced alteration of the tissues; not infrequently the tissue is broken down for a considerable distance (as may be the case with the brain).

If the hæmorrhage occur at the free surface of an organ the blood either escapes externally or is poured out into the cavity surrounding the organ.

Hæmorrhage from the mucous membrane of the nose is called *epistaxis;* vomiting of blood, *hæmatemesis;* bleeding from the lungs, *hæmoptoë* or *hæmoptysis;* from the uterus, *metrorrhagia* or *menorrhagia* (during menstruation); from the urinary organs, *hæmaturia*.

A collection of blood in the uterus is designated as *hæmatometra*, in the pleural cavity as *hæmothorax*, in the tunica vaginalis testis as *hæmatocele*, in the pericardium as *hæmopericardium*.

Recent extravasations of blood have the color characteristic of arterial or of venous blood. Later, the extravasate undergoes various alterations, which are particularly characterized by color-changes. Subcutaneous suggillations become first brown, then blue and green, and finally yellow. In course of time extravasates become absorbed again. (For more particular treatment of this subject, see the chapter on Hæmatogenous Pigment-formation, in Section IV.)

Escape of blood from the vessels occurs in two different ways. Sudden hæmorrhages are always connected with interruption in the continuity of the vessel-wall, and are therefore called **hæmorrhages per rhexin** or **per diabrosin.** This is the only form of arterial hæmorrhage. From the capillaries and the veins hæmorrhage may occur, on the other hand, in still another manner—to wit, **per diapede** [illegible] which the blood passes through the vessel [illegible] in the same. In this case the blood-co [illegible] another through the vessel-wall, while at the same time there is an escape of fluid; yet not of unaltered blood-plasma, but of fluid less rich in albumin (cf. § 44). Such hæmorrhages are often quite small and of inconsiderable extent; in other cases the process continues for a longer time, and the infiltration of the tissues with red blood-corpuscles becomes very extensive. Hæmorrhages by diapedesis are not always small, and hæmorrhages by rhexis not always great. Rupture of a capillary or of a small vein does not cause profuse bleeding; on the other hand, the escape of blood by diapedesis may attain to very great proportions. In a given case it is by no means always easy—indeed, it is often impossible—to make out whether hæmorrhage has taken place by rhexis or by diapedesis.

In suitable objects the phenomenon of diapedesis may be observed under the microscope. For this purpose we make use of the frog's mesentery or of the web of the frog's foot (Cohnheim). If before the examination we ligate the efferent veins, we see that the capillaries and the veins become gorged with blood. After a certain time the red blood-corpuscles begin to escape from the capillaries and the veins.[*] Hering[†] regards the process as one of filtration. As a result of obstruction to the outflow, the blood seeks to escape laterally and is forced through the vessel-wall by pressure.

Exhaustive investigations in regard to diapedesis of the red blood-corpuscles, as well as in regard to the escape of other anatomical elements within the blood-vessels, have been carried on by Arnold.[‡] He thought first that we must admit the presence of gaps in the endothelial tube at the points of exit of the corpuscular elements, and he designates these gaps as stigmata and stomata. He subsequently recognized the supposed openings to be but accumulations of the intercellular cement-substance between the endothelial cells. Under pathological conditions this cement-substance becomes softened and permits the passage of the red blood-corpuscles.

§ 46. The causes of **interruptions in the continuity of the vessel-walls** are partly *mechanical injury*, partly *increase in the intravascular pressure*, partly *disease of the blood-vessels.* Increase in the blood-pressure in the capillaries is sufficient of itself to cause capillary rupture without the aid of vascular changes, especially in cases of marked obstruction. Sound arteries and veins, on the other hand, cannot be dilated to the point of rupture by the mere rise of blood-pressure; diseased or abnormally thin-walled arteries, however, may burst. New-formed vessels are very fragile.

Diapedesis follows upon *rise of pressure in the capillaries and veins*, as well as upon *increased permeability of the vessel-walls.* If the outflow of venous blood in a given vascular area is totally interrupted, diapedesis of the red blood-corpuscles from the capillaries and veins starts up here and there; this is to be regarded as the result of the increase in intravascular pressure. The exodus of blood-corpuscles through vascular degeneration occurs particularly after mechanical, chemical, and thermal lesions of the vessel-walls, and we may suppose that certain *poisons* affect the vessel-walls with especial virulence. An abnormal permeability of the vessel-walls may, furthermore, be observed when, for a long period, the vessels have not been traversed by the blood-stream, and have suffered in their nutrition in consequence.

When an individual manifests a tendency to hæmorrhage the condition is called one of **hæmorrhagic diathesis**, of which we recognize a congenital and an acquired form.

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[*] Cf. Cohnheim, "Allgemeine Pathologie," I. Th., and *Virchow's Arch.*, 41. Bd.

[†] *Sitzungsber. d. Wiener Akademie*, 1868, 57. Bd.

[‡] *Virchow's Arch.*, 58., 62., and 64. Bd.

The **congenital hæmorrhagic diathesis** and **congenital hæmophilia**,* as has already been stated in §§ 30 and 31, belong to the hereditary diseases and have their cause probably in an abnormal constitution of the vascular walls, on account of which the afflicted subject has a marked disposition to bleed, and prolonged, uncontrollable hæmorrhages follow after petty injuries. It is nevertheless possible that the constitution of the blood is also in some way altered.

An **acquired hæmorrhagic diathesis** attends those diseases known as scurvy, morbus maculosus Werlhofii, purpura simplex, purpura (peliosis) rheumatica, purpura hæmorrhagica, and hæmophilia and melæna neonatorum, and furthermore plays a part in many infectious diseases and intoxications—e.g., septicæmia, endocarditis, malignant pustule, spotted typhus, cholera, smallpox, the plague, acute yellow atrophy of the liver, yellow fever, nephritis, phosphorus-poisoning, snake-bites, etc.—and also, finally, in pernicious anæmia, leucocythæmia, and pseudo-leucocythæmia. The cause of the diseases named in the first group—in all of which the occurrence of hæmorrhages in the skin, as well as in the mucous membranes, and in the parenchyma of other organs and tissues, constitutes a prominent symptom—is ordinarily supposed to lie in a *general disturbance of nutrition and circulation*, although many observations of the last few years make it probable that at least a great proportion of them belong to the class of *infectious diseases*. W. Koch is of the opinion that scurvy is an infectious disease, and that purpura in its many forms, and erythema nodosum, and the hæmorrhages occurring in the new-born, are varieties of the same infection. In the last few years bacteria have frequently been found in these latter affections also—that is, in purpura hæmorrhagica and also in hæmophilia neonatorum. In this connection we must refer particularly to the investigations of Kolb, Babes, Gärtner, Tizzoni, and Giovannini, who have found in those suffering from these diseases bacilli which were also pathogenic for the lower animals, and when injected produced an affection characterized by hæmorrhages. With these diseases those other infections which are characterized by hæmorrhages are probably connected, and it is to be supposed that the bleeding is produced partly by local changes in the walls of the vessels, caused by *localized growths of bacteria*, partly by the *injurious influence of toxic substances produced by the bacteria themselves*. In this case they should in part be reckoned among the hæmorrhages of intoxication.

The hæmorrhages occurring in conditions of anæmia are to be regarded as a consequence of anæmic degeneration of the vessels, though partly also as a result of disturbances of the circulation.

A whole list, finally, of apparently spontaneous hæmorrhages is connected with *irritation or paralysis of the vaso-motor nerves*, arising either from the central nervous system, or by reflex action, or through lesion of the conducting nerve-fibres. Here belong the hæmorrhage of menstruation, many forms of nasal, intestinal, and bladder hæmorrhage; furthermore, bleeding from the skin (stigmatization), from the breasts, from hæmorrhoids, from wounds, etc. Here also are to be reckoned a po tion of those pulmonary hæmorrhages which follow upon severe cerebral lesions, though in a particular case a trustworthy judgment often cannot be given, because disturbances of respiration, as also the aspiration of irritating substances into the lungs, may likewise lead to hyperæmia and to the escape of blood in the lungs. Lastly, there occur in brain-disease —particularly in disease of the crura cerebri—gastric and intestinal hæmorrhages which are dependent upon the cerebral lesion. According to von Preuschen, the gastric and intestinal hæmorrhages occurring during the first days of life, and known as melæna neonatorum, belong to this category, inasmuch as during labor hæmorrhages and ecchymoses are not infrequently produced in the brain, in consequence of which the intestinal hæmorrhages follow. By others, on the contrary (Gärtner), melæna neonatorum is classed among the infectious diseases.

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* The wording of the original text clearly mak [illegible] rate diseases; and yet it would seem as if the " [illegible] an "or," the text then reading—"congenital h [illegible] hæmophilia."—TRANSLATOR'S NOTE.

§ 47. When an **artery is suddenly closed** by thrombosis, or by embolism, or by ligation, or by any other means, there occurs behind the obstructed point, as has already been stated in § 38, an arrest of the circulation, after the vessel has more or less emptied itself by the contraction of its walls; while from the point of obstruction back to the point of divergence of the nearest arterial branch the blood-pressure increases. If the branches of the artery behind the point of obstruction have free arterial communication with some other unobstructed artery, this latter by becoming dilated is able to carry a supply of blood sufficient for the

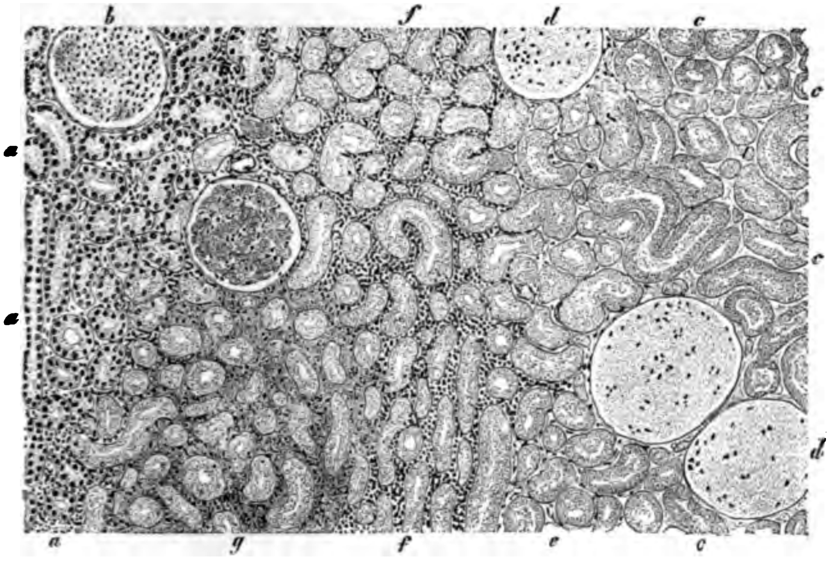

FIG. 21.—Part of the edge of an anæmic infarct of the kidney. *a*, Normal uriniferous tubules in a normal stroma; a_1, Normal uriniferous tubules in a stroma infiltrated with cells; *b*, Normal glomerulus; *c*, Necrotic tissue without nuclei, with granular coagula in the tubules; *d*, Necrotic glomerulus, swollen and with few nuclei; *e*, Uriniferous tubules without nuclei, in a stroma with nuclei still persisting; *f*, Necrotic tissue with cellular, and, *g*, with hæmorrhagic infiltration. (Specimen hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 50 diameters.)

area of distribution of the obstructed vessel, and the arrested circulation is thus restored.

If the obstructed area has no vascular connections through which it can draw its blood-supply, that portion of tissue which is thus deprived of its nutrition remains empty of blood and dies; thus there is formed an **anæmic infarct.** Parenchymatous organs, such as the spleen and the kidneys, in those portions which are deprived of blood, appear cloudy, opaque, yellowish white, often clay-colored, and the microscope shows that the tissues are dead, and that therefore the nuclei of the cells (Fig. 21, *c*, *d*, *g*) no longer take the stain.

If the area of distribution of the obstructed vessel have no arterial anastomoses, if the obstructed vessel be, to use Cohnheim's expression, a **terminal artery**, but if there remain, on the other hand, the possibility of a scanty afflux of blood from adjacent capillaries or from the veins, a **hæmorrhagic infarct** may be formed. The capillaries of the region rendered anæmic by the obstruction become slowly filled once more with blood, which comes in part from the domain of adjacent vessels, in part from the veins, from which it flows in a retrograde direction. The blood flowing in from the adjacent capillaries is under very low pressure, which does not suffice to drive the blood promptly through the obstructed area into the veins; the blood consequently stagnates and the capillaries become filled fuller and fuller. Even in the event of a possible reflux of blood from the veins, the blood, of course, merely flows into the capillaries, but does not circulate through them.

In consequence of the *stagnation* which arises from the lack of power to force the blood along, diapedesis eventually takes place. The escape of the blood is favored by the *disorganization and necrosis of the tissues and of the vessel-walls*—changes which result from the arrest of nutrition

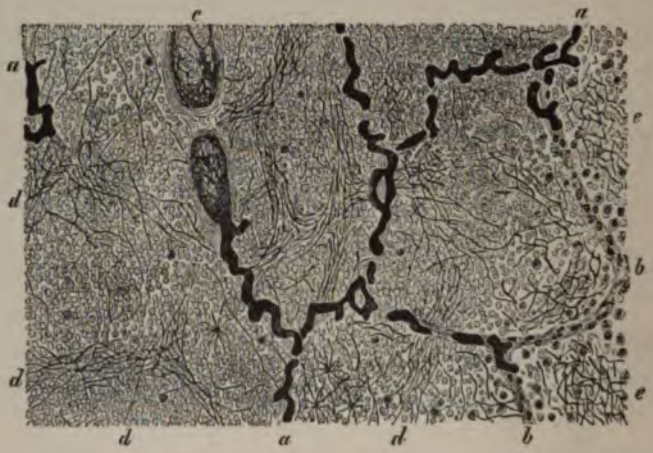

FIG. 22.—Part of the edge of a recent hæmorrhagic infarct of the lung. *a*, Interalveolar septa without nuclei, containing capillaries gorged with thrombotic masses, homogeneous in appearance and deep-bluish violet in color; *b*, Septa containing nuclei; *c*, A vein with a red thrombus; *d*, Alveoli completely filled with clotted blood; *e*, Alveoli filled with serous fluid, fibrin, and leucocytes. (Specimen hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 100 diameters.)

or its reduction to almost *nil*—and it is further favored by the *coagulation* which occurs in the efferent vessels and renders impossible the onflow of the blood. The ultimate effect of the diapedesis is the permeation of the whole tissue with coagulated blood (Fig. 22, *d*), and the formation of a solid, ***reddish-black hæmorrhagic focus***, generally conical in shape.

Embolic hæmorrhagic infarcts are to be found *in the lungs* (Fig. 22), but they are formed, after the embolic obstruction of an artery, *only when there is a tendency to stagnation of the pulmonary circulation;* while with a normal pulmonary circulation such circulatory disturbances as follow upon embolism are generally promptly allayed. In the corporeal circulation extensive hæmorrhages from embolism are confined, almost exclusively, to the territory of the superior mesenteric artery, whose branches, although they are not terminal vessels, yet possess but few anastomoses. ***Anæmic infarcts*** occur particularly *in the spleen, in the heart, in the kidneys, and in the retina*, though hæmorrhage is found in these also, along the borders of the obstructed region, so that the bloodless foci have a hæmorrhagic border surrounding them, or at least present hæmorrhagic spots (Fig. 21, *g*). The necrotic tissue, furthermore, becomes saturated with fluid, and may then swell (Fig. 21, *d*) and present granular or fibrous coagula in its interstices (Fig. 21, *c*). In case of the obstruction of arteries of the brain, or of those of the extremities, or of the central artery of the retina, hæmorrhages may also occur in spots. In the interior of the infarct the tissues are generally wholly or in greater part dead, and it is especially the specific elements of the affected organ which are the first to die. After a time exudative inflammation arises in the neighborhood of ischæmic and of hæmorrhagic infarcts, with the formation of a cellular (Fig. 21, *f*) or fibrocellular exudate (Fig. 22, *e*); and this is followed by tissue-proliferation (Fig. 16, *c*, *d*, page 126), by means of which the dead tissue, with its hæmorrhagic infiltration, becomes absorbed (Fig. 16, *a*, *b*), and its place is taken by connective tissue.

In his published works Virchow, who was the first to institute any profound experimental researches into the matter of thrombosis and embolism, left the question of the origin of the hæmorrhagic infarct still open, but he expresses the opinion that in the area of distribution of the obstructed artery the vascular walls suffer certain alterations which render them more fragile and permeable. If a collateral circulation afterward become established, this secondary hyperæmia causes exudation and extravasation. Cohnheim, who observed directly under the microscope the results of embolism in the frog's tongue, demonstrated the retrograde flow of the blood in the veins, the refilling of the capillaries, and the escape of the blood by diapedesis. The cause of the diapedesis he thought was essentially the disorganization of the vascular wall due to the anæmia. Litten considers the reflux of the blood from the veins to be but an unessential part of the phenomenon, and ascribes the refilling of the exsanguinated area to the pouring in of blood from the neighboring vascular fields. The disorganization of the vessel-walls he thinks also unnecessary for the production of infarction, inasmuch as the stagnation suffices of itself, just as in venous obstruction, to explain the diapedesis. The diapedesis is therefore increased whenever in such foci the blood coagulates in the efferent veins.

Von Recklinghausen considers the principal cause of the formation of a hæmorrhagic infarct to be the hyaline thrombosis of the capillary vessels of the region involved by the embolism. If subsequently blood from neighboring vessels enters the still pervious portions of the implicated territory, it encounters resistance, becomes stagnant, and then escapes from the vessels. According to Klebs[*] emboli thrown into the circulation of the lower animals cause infarction only when blood rich in ferment is thrown in after the embolus, or else when substances provoking coagulation become disseminated through the obstructing plug.

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[*] *Schweizer Arch. f. Theirheilk.* 28. Bd., 1886.

Grawitz is of the opinion that hæmorrhagic infarcts of the lungs are never to be ascribed to vascular obstruction by embolism, but rather that stagnation and pulmonary inflammation are to be regarded as the cause of the hæmorrhages. He furthermore regards the new-formed vessels consequent upon the inflammation as the essential source of the hæmorrhage, and views the coagula in the pulmonary arteries, not as emboli, but as thrombi of autochthonous origin.

According to my own views, which are shared by the great majority of pathologists, there is no room to doubt the existence of embolic pulmonary infarcts. They can only occur, it is true, when there is a tendency to stagnation in the lungs, and therefore, in animals with unimpaired pulmonary circulation, they are not to be provoked by the introduction of obstructing particles into the pulmonary arteries. The essential causes of the escape of the blood are to be found in the stagnation of the blood within the obstructed area, and in the necrosis of the tissues as well as of the vessels themselves. This last may be positively recognized in the disappearance of the nuclei (Fig. 22, *a*). Secondary thromboses in the vessels within the area of obstruction are frequent, and increase the extent of stagnation and of extravasation; they are not, however, invariably present at the time of the extravasation, and are therefore not essential to the occurrence of the hæmorrhage. Hæmorrhages also occur frequently in the lungs, particularly in subjects with cardiac disease, merely as the result of impeded circulation; these are not always inconsiderable, but are often, indeed, extensive, and, as they are limited to a circumscribed area, they have very much the appearance of embolic infarcts. They are generally, however, less sharply defined and less firm, so that they are for the most part easily distinguishable from embolic infarcts.

VI. Lymphorrhagia.

§ 48. **Lymphorrhagia** occurs when the continuity of a lymphatic vessel becomes interrupted at a certain point and the lymph is poured out into the surrounding parts. As the pressure in the lymphatics is very low—that is, is not greater than in the surrounding tissues—it follows that lymph can be poured out from a lymphatic only when the affected vessel lies on the external surface, or when a natural cavity is at hand into which the lymph can flow, or when, by the same cause which effected the breach in the lymph-vessel, an open space was formed in the tissues. So, for example, in wounds we may see lymph escaping along with the blood, but the outflow is checked upon the least resistance. If after the wounding of a lymphatic vessel the aperture persists, so that there is a permanent flow of lymph escaping externally (as is the case in ulcers) or into one of the cavities of the body, we have a so-called **lymph-fistula,** through which considerable quantities of lymph may become lost. Most important and also most dangerous is a *division of the ductus thoracicus,* observed sometimes after traumatism, and occasionally also as the result of obstruction to the lymph-flow at some point through compression of the duct (after inflammation, or in the course of the development of tumors). The lymph is poured out into the thoracic or the abdominal cavity, and a *chylous hydrothorax* or a *chylous ascites* ensues.

In very rare cases it happens that the urine, as it comes from the bladder, has the appearance of a milk-white, or a yellowish, or, through the admixture of blood, a reddish emulsion, and contains, along with albumin, large quantities of fat subdivided into very minute globules. The phenomenon is consequently known as **chyluria.** It occurs endemically in certain tropical regions (Brazil, India, the Antilles, Zanzibar, Egypt), where it is caused by a parasite, the *Filaria Bancroftii*, which inhabits the abdominal lymph-vessels and there produces its embryos (*Filaria sanguinis*); these, during the repose of the patient in the horizontal posture, swarm in great numbers in the blood and are also contained in the chylous urine. The connection between the chyluria and the invasion of the lymph-vessels by the Filaria has not yet been satisfactorily demonstrated by anatomical investigations; it is nevertheless probable that, on account of the obstruction which occurs in the lymph-circulation, chyle escapes from the ruptured lymphatics of the bladder and mingles with the urine, so that the chyle-like fluid does not come from the blood and through the kidneys (Scheube, Grimm); and in corroboration of this view we may mention the facts, first, that upon autopsy the abdominal lymphatics exhibit marked dilatation (Havelburg), while the kidneys are but slightly altered, and second, that, according to an observation of Havelburg's, the urine coming directly from the ureter showed no admixture of chyle, although chyluria was present at the time.

SECTION IV.

Retrograde Disturbances of Nutrition and Infiltrations of the Tissues.

I. On Retrograde Disturbances of Nutrition and Infiltrations of the Tissues in General.

§ 49. **Retrograde disturbances** are characterized in general by *degeneration of the affected tissue*, often with *diminution in its size* as a whole and *disappearance of its elements.* Accompanying this there is *disturbance of the function of the tissue.*

Infiltrations of the tissues are characterized, on the other hand, by *a deposit in them of pathological substances* which are either formed in the body itself or have been introduced into it from without. In this case, also, the *function of the tissue is usually interfered with.* The infiltration is often only a result of preceding degenerative changes, or, on the other hand, it may itself represent the principal manifestation of this degeneration.

Retrograde disturbances of nutrition may affect the body in its completely developed form or during its period of development and growth, and in either case they lead to an abnormal smallness of the affected organ or portion of the body. In the former case this diminution in size depends upon disappearance of the fundamental elements of the affected tissue, and is designated **atrophy.** In the latter case, on the other hand, it depends upon an imperfect development of the affected organ, shown by a more or less rudimentary condition of its elements. If in this way an organ or portion of an organ entirely fails of development, so that it is either completely absent or at most only a mere rudiment of it is present, the condition is spoken of as **agenesia** or **aplasia.** But if the affected portion of the body is only moderately below the norm in its development, the condition is spoken of as **hypoplasia.**

The **causes of agenesia and of hypoplasia** may be either intrinsic or extrinsic—that is to say, the diminished size and imperfect formation of the organ may depend on pathological conditions within itself, or they may be the result of the action of injurious external influences. The maldevelopment may further affect either the entire body, in which case a *dwarf* results, or it may affect a portion of it only, giving rise then to *imperfect formation of single parts or organs.*

The **causes of degeneration of tissue and of the resulting atrophy** are for the most part injurious extrinsic influences to which the tissue is exposed during life, and yet at times they may also be traced to intrinsic conditions. This latter is notably the case with the tissues during old age, when they are reaching their physiological limit and are gradually becoming incapable of properly nourishing and preserving themselves. In many tissues a similar retrograde change, dependent upon intrinsic causes, occurs earlier in life, as, for example, physiologically in the ovary and in the thymus gland.

Among the extrinsic harmful influences which may lead to degenerations nearly all those should be mentioned which have been discussed in Section II. Thus an important part is played by disturbances of the circulation, with imperfect transport of oxygen and nutriment to the tissues, and by poisons. Usually *degenerations are of limited extent*, so that one speaks of **degenerations of special tissues or of particular organs**; but, on the other hand, *disturbances of nutrition may be more general* and the entire organism may suffer. Thus the picture of a general disease may be produced by a degenerative or atrophic condition of the blood, which may show itself either by diminution of the red blood-corpuscles or of their hæmoglobin content, whereby a permanent condition of **general anæmia** or **insufficient blood-supply** is induced, the nutrition of the tissue being correspondingly impaired.

Again, as the result of an insufficient ingestion of food or of disordered assimilation on the one hand, and of excessive waste of proteids and fats of the body on the other, there may result a condition of weakness and malnutrition, often associated with anæmia, leading to atrophy of the body as a whole. This is spoken of as **cachexia** or **marasmus**. If, under these circumstances, it appears likely that certain substances are undergoing formation in the body which, when taken into the blood and various fluids, act as impurities and alter the constitution of those fluids, the condition is spoken of as one of **dyscrasia**.

II. Death.

§ 50. All life comes sooner or later to an end—to death. When this occurs at an advanced age, without preceding well-defined symptoms of disease, it may be regarded as the normal termination of life, and is to be attributed, at least in part, to the cessation of function of certain of the organs necessary to the continuance of life. This occurs usually as the result of intrinsic causes, although in most cases it is impossible to exclude the influence of extrinsic conditions in bringing about the cessation of function of the organs in question.

When death occurs early in life—that is to say, at an age earlier than the average age of death in man—and when it is preceded by symptoms of disease, it must be considered abnormal. Its occurrence under these circumstances is for the most part referable to extrinsic influences, though it may occasionally be due to intrinsic inherited conditions. It is obviously impossible to draw any sharp line of separation between what may be called physiological and pathological death.

The causes of pathological death are those which have been discussed in Section II. as the causes of disease.

A body is said to be dead all of whose functions have forever ceased. Death is, however, inevitable at that instant when one or more of the functions imperatively necessary to life have ceased, although it is not necessary that at that moment *all* functions shall have ceased. Indeed, after life is irrevocably lost, many organs are still capable of performing their function, and it is only after a little time that all the organs die. Thus the life of the organism passes gradually, by the progressive cessation of the functions of its various organs, into the state which we term death.

The discontinuance of the functions of the heart, of the lungs, and of the nervous system results in almost immediate death of the entire organism. Discontinuance of the functions of the intestine, of the liver, and of the kidneys renders life impossible after a certain length of time, often measured by days. Destruction of the organs of reproduction in no wise endangers either the health or the life of the affected individual, and, similarly, one or more of the organs of special sense may be spared.

Death is usually inevitable after cessation of respiration, and certain after cessation of the heart-beat. With discontinuance of breathing it is impossible for any organ to continue alive longer than a very short time. The stoppage of the heart similarly makes impossible any further nourishment of the tissues, and the central nervous system quickly becomes unable to continue the performance of its functions.

After death the body may present considerable diversity of appearance. The distribution of the blood at the time of death has much to do with the aspect of its visible portions. Thus an abundant supply of blood in the skin causes it to have a bluish-red color, while if anæmic it is pale. Furthermore, disease may materially alter the appearance of the exterior of the body.

Sooner or later after death certain changes occur in the tissues of the body which may be regarded as **unquestionable signs of death.** In the first place, *the temperature of the body falls*, so that after a variable interval it reaches the temperature of the surrounding air. It should, however, be borne in mind that the temperature at times does not begin to sink immediately after death, but first rises somewhat. The rapidity of the cooling of the body depends partly upon the character of the body itself and partly upon the nature of its surroundings. The time required may vary from one to twenty-four hours.

The *coldness of the dead* is spoken of as *algor mortis*.

At the time of death the skin is usually pale, but after a variable period —from six to twelve hours, or even less—bluish-red blotches appear on the dependent portions of the body. These are designated *livores mortis* or *blotches of cadaveric lividity*, and depend upon the accumulation of the blood in the capillaries and veins of the more dependent portions of the skin. They are not observed in those parts of the body subjected to pressure. Their number and size depend upon the amount of blood in the skin at the time of death. Parts which have been cyanotic in life may retain this appearance after death; this is particularly the case with the head, the fingers, and the toes. The color of these blotches of cadaveric lividity is for the most part bluish red, and there may be considerable difference in the intensity of their coloring. In cases of poisoning by carbon monoxide it is bright red.

The weight of the body causes flattening of those muscular parts of the body upon which it rests.

Sooner or later there occurs *a cadaveric stiffening of the muscles*, to which the term *rigor mortis* is applied. This is characterized by contraction of the muscles, which, according to Bruecke and Kuehne, is dependent upon the coagulation of their contractile substance. It makes its appearance usually in from four to twelve hours after death, though it may occur almost immediately thereafter, or may not appear until twenty-four hours have elapsed. It usually is first noticed in the muscles of the jaw, throat, and neck, and extends from them to the trunk and extremities. After from twenty-four to forty-eight hours it usually disappears, but may occasionally persist for several days.

This rigor mortis affects the smooth muscle-fibres as well as the striated. The contraction of these elements in the skin is the cause of the so-called goose-flesh of the cadaver.

Putrefaction begins somewhat before the disappearance of rigor mortis. It is evinced by its peculiar odor, by change in color of the skin and of the mucous membranes, and by change in the consistence of the tissues. Much influence upon the commencement and progress of putrefaction is exerted by the condition of nutrition of the body, by the nature of the disease which has preceded death, and by the nature of the surrounding medium, especially the temperature. Occasionally putrefactive changes occur in portions of the body which are dead even before the death of the entire body; and in cases in which putrefactive bacteria are present in the body at the time of death putrefaction may begin immediately thereafter.

As an early sign of putrefaction there is usually greenish discoloration of the skin, commonly appearing first over the abdomen. With the progress of putrefaction the unpleasant odor and discoloration increase, and gases are formed in the intestine, in the blood, and in the tissues, which at the same time become soft and friable.

Shortly after death *the cornea becomes lustreless and clouded, the eyeball loses its prominence*, and *dark spots* after a time *develop in the sclera*. These changes in the eye are due to evaporation and putrefaction. When the eyelids are not closed the *results of drying are very evident in the uncovered portions of the eyeball.* Wherever the skin has lost its epidermis the exposed tissues become dried.

Under certain circumstances the evidence of life may be reduced to a minimum, and a condition of **apparent death** may result which may be mistaken for death. Post-mortem lividity, rigor mortis, and evidences of putrefaction are unmistakable signs of death; but, since these changes do not appear until some time after death, an interval is left during which it may occasionally be doubtful whether death has actually taken place or not. To ascertain the truth with certainty under these circumstances it must be determined by an appropriate examination whether the heart still beats, whether respiration is going on, whether the blood still circulates, and whether the nerves and muscles still remain irritable.

This condition of apparent death may occur under a variety of circumstances, as, for example, in the course of cholera, in catalepsy, in hysteria, after great bodily exertion, after violent concussion of the nervous system, after profuse hæmorrhage, when respiration is suspended as the result of strangulation, hanging or drowning, in certain cases of poisoning, in lightning-stroke, after prolonged exposure to cold, etc. The duration of this condition is usually short, but it may occasionally persist for hours or even days.

III. Necrosis.

§ 51. By **necrosis** is understood a condition of *local death*, or death of single cells and groups of cells. As the result of necrosis there is always a cessation of the functions peculiar to the affected tissue.

It is only occasionally that the necrosis of a cell-group or of an entire organ makes itself at once evident in recognizable changes of structure; that is to say, the slight histological changes which the cells undergo as the result of their death do not permit us always to determine with certainty the moment of the cessation of their life, nor does the macroscopic appearance of the visible portions of the body inform us when a portion thereof becomes necrotic.

Necrosis of a tissue is therefore evident upon anatomical examination only when certain changes in its structure have occurred either coincidently with its death or subsequently thereto. The immediate occurrence of such changes is met with occasionally in the case of traumatism, while the changes which develop later always make their appearance after the lapse of a certain length of time. It is customary to distinguish several forms of necrosis, according to the nature of the changes which take place.

Histologically necrosis of a cell is very often indicated by its protoplasm taking on a homogeneous appearance and by disintegration and disappearance of its nucleus. The chromatin of the latter—the substance which is stained by the nuclear dyes—forms small masses and granules which occasionally leave the nucleus and get into the cell-body, where they dissolve and disappear. In other cases the nucleus first loses its power of staining, and then gradually dissolves and disappears (Fig. 23, *c*), so that even in well hardened and stained preparations there may be no trace whatever of the nucleus. Thus, for example, in those portions of the spleen or kidney which have been rendered ischæmic by the cutting off of the blood-supply in embolism of the arteries of these two organs, the nuclei of the cells of the spleen and of the kidney epithelium (Fig. 21, *c*) are very soon lost, and at the same time the affected tissues assume a distinctly pale, cloudy, yellowish-white appearance, which makes it possible to recognize the onset of necrosis even with the naked eye.

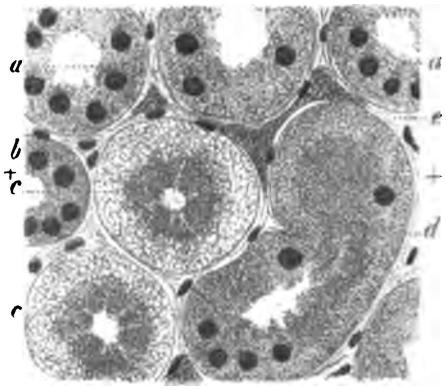


FIG. 23.—Necrosis of the epithelium of the uriniferous tubes in a case of icterus gravis. *a*, Normal convoluted tubule; *b*, Ascending looped tubule; *c*, Convoluted tubule with necrotic epithelium; *d*, Convoluted tubule with only a part of its epithelium necrotic; *e*, Stroma and blood-vessels, as yet unaltered. (Preparation hardened in Müller's fluid, stained with gentian violet, and mounted in Canada balsam. Magnified 300 diameters.)

The injuries which lead to death of limited portions of the body may be classed in three groups. The first includes those which destroy the tissue directly through **mechanical violence** or through the **action of chemicals.** Thus, for example, a finger may be crushed by violence, sulphuric acid may destroy a portion of the skin, or bacteria may cause the destruction of glandular tissue in which they develop. The second group of **injurious influences are of a thermal character.** Elevation of the temperature of a tissue for any length of time to 54–68° C. results in its death. Higher temperatures act more quickly. Similarly, excessive cold can be borne for only a short time (cf. § 5). A third form of necrosis, characterized as **anæmic necrosis** or as **local asphyxia**, is the result of **discontinuance of the supply of nourishment and oxygen to the tissues.**

In addition to these, many authors distinguish as a special group those forms of necrosis which result from lesions of the central nervous system or of the peripheral nerves, and which may be designated as **neuropathic necroses.** By some this form of necrosis is believed to be the direct result of lesion of the trophic nerves, while by others it is attributed to changes in the circulation and to the effects of pressure and mechanical injury of anæsthetic and paralyzed portions of the body. The observations thus far made upon man, and experiments upon animals, indicate that, at all events, an important part in the production of this form of necrosis is always played by external injuries and by disturbances of the circulation, more particularly by spasm of the vessels.

Again, all those conditions seriously affecting the circulation and leading to stoppage of the blood-supply—such as thrombosis, embolism, closure of a vessel as the result of lasting abnormal contraction, disease of its wall, or ligation, pressure on the tissue, inflammation, hæmorrhage, etc.—may result in necrosis of the affected part; nor is it necessary that the disturbance of the circulation be permanent, since a comparatively transient interference with the blood-supply may be followed by death of tissue. Whether or not hæmorrhage occurs in such cases, as was stated in § 47, would appear to be immaterial to the result, influencing only the appearance of the diseased tissue. *Hæmorrhagic infarction* has therefore precisely the same significance as an *anæmic necrosis combined with hæmorrhage.*

When death of a tissue supervenes quickly upon the infliction of an injury, it is called **direct necrosis**; when it occurs slowly, and is preceded by degenerative changes in the tissue, it is termed **indirect necrosis** or **necrobiosis.**

Mechanical, chemical, and thermal injuries and anæmia may exert their effect coincidently in the production of necrosis, or they may act separately, one after the other. When the tissue is damaged by either of the three injuries first named, the blood itself also frequently undergoes a change, which terminates in stasis and coagulation of this fluid in the capillaries, as well as in the veins and arteries; and as a result of this the circulation is arrested.

Whether or not any given injury will cause necrosis does not depend wholly upon its nature and severity, but is influenced to a considerable degree by the condition of the affected tissue at the time of the occurrence. Thus, if a tissue has been subjected for a long time to the depressing influence of an impaired circulation, or if its vitality has been lowered by marasmus or hydræmia or a diseased condition of the blood, it dies much more easily than if it had been previously healthy. As an example of this may be cited the frequency of necrosis after comparatively slight injuries, more particularly of the extremities, in the aged and in those who suffer from uncompensated valvular lesions of the heart. Furthermore, disturbances of the nerves of the vessels, in so far as they lead to impairment of the circulation, may afford a predisposition to necrosis

In the prostration incident to typhoid fever, comparatively slight pressure on the hip, elbow, sacrum, or heel may be sufficient to bring about gangrenous destruction of the skin and of the subcutaneous tissue. These forms are known as **senile** and **marasmic necroses,** or as **marasmic gangrene** and as **decubitus.**

The structure of the tissue, its position, the manner of its death, and the causes of the necrosis, all exert a determining influence upon the **course of the necrosis,** that is to say, upon the changes in the tissue which will result therefrom. An important influence is also exerted by the amount of blood and lymph in the tissue, and bý the opportunity for access of the air and of the ferments of putrefaction.

Not without influence, also, are alterations in the tissue which may have antedated the onset of necrosis—as, for example, fatty degeneration, inflammation, hæmorrhage, etc. Under these circumstances, even when the progress of the necrosis is simple and is marked by comparatively slight histological changes, the resulting structural changes may be very complex. The varieties of necrosis thus induced will be discussed in succeeding paragraphs.

As the **result of necrosis** there is always *inflammation of more or less intensity in the surrounding tissue* (cf. Figs. 21 and 22), and it is most intense when processes of decomposition set up in the necrotic tissues. Through the formation of a zone of inflammation the necrotic area is shut off from the surrounding tissue—is isolated and sequestered; and the *inflammation is accordingly spoken of as limiting or sequestering,* and the dead tissue thus shut off is termed a *sequestrum.* A detailed description of these inflammatory processes will be found in Section VI.

If we exclude from consideration for the present the more special complications of necrosis—as, for example, the development of specific irritating materials—four **sequelæ** are to be distinguished: 1. The dead tissue may be completely *absorbed,* or may be *cast off* from a surface, and *its place taken by newly formed normal tissue.* This is spoken of as *regeneration.* 2. The dead tissue is similarly removed, but, instead of the normal tissue of the part being reproduced, simple connective tissue, the so-called *cicatricial tissue,* more or less completely supplies the defect. 3. The dead tissue is only partially absorbed or cast off, and *a sequestrum of necrotic tissue remains,* which may later become calcified, and which is in time surrounded by a dense connective-tissue capsule. 4. There is *cyst-formation* at the site of the necrosis, resulting from encapsulation of the dead tissue by connective tissue, absorption of the necrotic mass, and substitution for it of a liquid, which fills the space within the capsule and thus forms a cyst. This result of necrosis is most often met with in the brain, and the reader is referred, for further details regarding it, to the chapter on Softening of the Brain [in the volume devoted to special pathological anatomy].

The time required for the induction of necrosis after stoppage of the circulation varies with the different tissues. Ganglion-cells, renal epithelium, and the epithelium of the intestine die in so short a time as two hours, while skin, bone, and connective tissue may remain alive for twelve hours or more. In general it may be stated that all tissues performing special functions die much sooner than those, such as connective tissue, which have only themselves to sustain.

The cause of the above-described changes in, and final disappearance of, the nuclei in necrotic areas is found in the infiltration of the necrotic tissue with lymph from the surrounding tissue; and these changes are consequently absent when, for any reason, the circulation of the lymph in the diseased organ is stopped. Putrefaction is also a potent influence in inducing a rapid disintegration and disappearance of the nuclei; but Fr. Kraus has shown that portions of tissue preserved aseptically and out of all contact with bacteria, in moist chambers at the body-temperature, lose their nuclei after a time. The tissue of the liver most quickly shows this change (Goldmann), while it may not appear in the spleen and kidney until much later, and all nuclei may not have disappeared even after the lapse of from eight to fourteen days. It has been found by Goldmann that the disappearance of the nuclei occurs only in the presence of a considerable degree of moisture, and may be prevented by desiccation of the tissue.

§ 52. When a tissue which is dead or dying contains coagulable materials and the necessary ferments, coagulation occurs, provided no conditions are present that may prevent such action; and the term **coagulation necrosis** has consequently been applied to this variety of necrosis (Cohnheim, Weigert). Such coagulation may occur in liquids in which degenerating and disintegrating cells afford the necessary ferment, and we must consequently group among the coagulation necroses the *coagulation of the blood* described in § 39 and the consequent formation of thrombi. As a rule, coagulation occurs particularly in *exudates* from the blood-vessels in the course of inflammation. Here the coagulated material appears as flocks or as a false membrane, when the inflamed tissue is a mucous membrane (Fig. 24, *a*) or a serous membrane, or as granular or fibrillar masses lying in the liquid of the œdematous tissue.

In inflammatory false membranes the *fibrin* may be present as fine granules, as fibrils, as thicker fibres forming an interlocking framework, or as homogeneous masses.

Fig. 24.

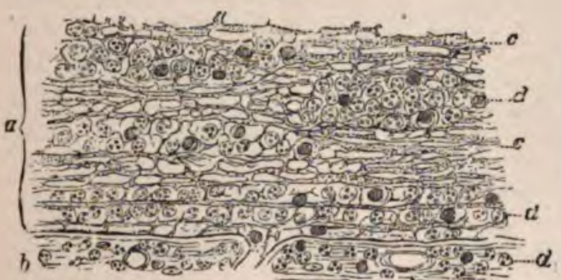


FIG. 24.—Croupous membrane from the trachea. *a*, Transverse section of the membrane; *b*, Uppermost layer of the mucous membrane, with pus-cells, *d*,[1] scattered throughout its substance; *c*, Fibrin threads and granules; *d*, Pus-cells. (Magnified 250 diameters.)

Fig. 25.

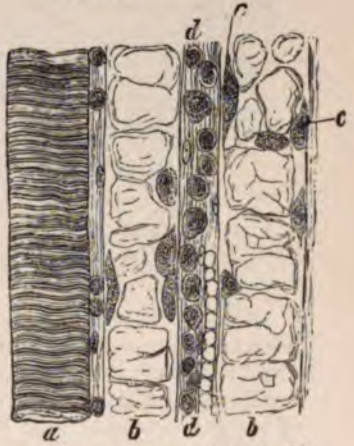


FIG. 25.—Waxy degeneration of muscular fibres, from a case of typhoid fever. *a*, Normal muscular fibre; *b*, *b*, Degenerated fibres, which have broken down into separate masses; *c*, *c*, Cells lying inside of the sarcolemma; *d*, Connective tissue infiltrated with cells. (Magnified 250 diameters.)

A second form of coagulation is observed when *dead cellular masses* lying within the parenchyma of the body *become infiltrated with lymph containing fibrinogen*. Under these circumstances the cells become changed into finely granular masses (Fig. 23, *c*) or into hyaline bodies (Fig. 25, *b*; Fig. 26, *b*), while at the same time they lose their nuclei. This variety of coagulation necrosis is most often met with in *ischæmic infarctions* of the kidney (Fig. 21) and spleen, already described in § 47, in which the cells appear as finely granular masses, devoid of nuclei, between which—for example, in the lumina of the tubules, in the case of the kidney—fibrillar and hyaline masses are found. It occurs also in many toxic and traumatic necroses of the glandular organs, and in the necrosis of muscle-tissue which results from thermal, traumatic, or chemical injuries. In the last-mentioned form of necrosis the muscle loses its striations, and its contractile substance becomes converted into shining, homogeneous material, which may later become broken into irregular hyaline masses (Fig. 25, *b*). A muscle which has undergone this change appears of a pale, grayish-red color, similar to the flesh of fish, and is more cloudy and drier than normal. Zenker has applied the name "waxy" to this variety of degeneration.

Finally, similar processes of coagulation are of frequent occurrence in cellular inflammatory exudates, in which the cells of the tissue, as well as the exuded ingredients of the blood, undergo coagulation into irregular granular or homogeneous masses devoid of nuclei. As the result of this process considerable masses of tissue may become wholly devoid of nuclei (Fig. 26, *b*) and appear granular (cf. Section VI.). The tissue which has thus died presents a grayish or yellowish-white appearance, which may be browner if it contains altered blood, or somewhat greenish if putrefactive changes have occurred.

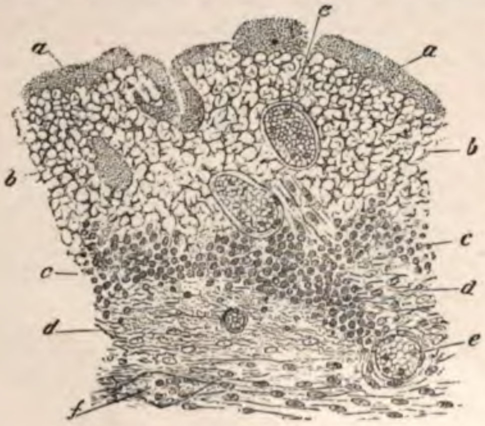


FIG. 26.—Section of a uvula after the destruction of its epithelial covering by diphtheria. *a*, Micrococci; *b*, Mucous membrane which is infiltrated and broken down into separate masses; *c*, *c*, Parts infiltrated with small cells; *d*, Fibrinous exudation; *e*, Blood-vessels; *f*, Lymph-vessels containing cells and fibrinous material. (Bismarck-brown preparation. Magnified 100 diameters.)

Besides the cells, the interstitial connective tissue, the walls of vessels, hyaline membranes, etc., may become swollen as the result of imbibition of liquid, and may then coagulate into a homogeneous mass; and at the same time granular, fibrillated, and hyaline products of coagulation may also be formed in the spaces between the fibres of a tissue.

§ 53. The term **cheesy degeneration** is applied in pathology to a change in the tissue as the result of which it comes to have the gross appearance of firm cheese or of softer cream-cheese. This term has been chosen solely because of the gross appearance of the product of the degeneration, for it is known that the processes underlying it are not always the same.

In the first variety of cheesy degeneration—that which results in the formation of a firmer, dry, rather tenacious, yellowish-white, highly refracting material—we have to do with a special form of **coagulation necrosis**, which occurs most frequently in tissues rich in cells—as, for example, in tubercular tissue, in some very cellular tumors, and in lung-tissue infiltrated by the products of inflammation. The death of the tissue usually takes place rather slowly, so that the process has perhaps more the character of a gradually progressive degeneration, or **necrobiosis**, than that of a true necrosis.

Tissue which has become completely cheesy is always devoid of nuclei. It is sometimes *finely granular*, at other times more *homogeneous and shining*. In the transition of a tissue into these cheesy masses the change takes place in one of three ways: it either acquires a more and more homogeneous appearance and finally loses its nuclei; or irregular small masses of homogeneous material (Fig. 27, *a*) form, which later become conglomerated; or, finally, there is a disintegration of the cells, as the result of which granules and fine granular fibres (fibrin) are formed, which then become agglomerated into a dense homogeneous mass. This last mode of formation is observed more particularly in cheesy exudates in the lungs, while the first is of frequent occurrence in tissues which have undergone hyperplasia as the result of chronic inflammation or of tubercle-formation (Fig. 27). Masses which were originally homogeneous may become granular after a time, as the result of further changes (Fig. 27, *a*).

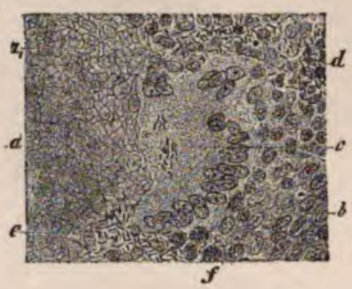


FIG. 27.—Tissue from a focus of tubercular disease, showing bacilli and a limited area of cheesy degeneration. *a*, Granular cheesy material; a_1, Cheesy material in the form of small separate aggregations; *b*, Fibrocellular tissue; *c*, Partly necrotic giant cell, with bacilli; *d*, Cellular tissue invaded by bacilli; *e*, A similar invasion in tissue that is necrotic; *f*, Bacilli inclosed in cells. (Preparation treated with fuchsin and aniline blue, and mounted in Canada balsam. Magnified 200 diameters.)

In the *softer variety of cheesy matter*, which is rather whiter in color, the bulk of the substance is made up of *fatty and albuminous detritus, of granules, or of irregularly shaped fragments* of broken-down tissue. All cells or traces of cells have disappeared. This substance owes its opacity and light color to its large content of fat-droplets.

The two varieties of cheesy degeneration which are distinguished the one by its firmer and the other by its softer product, are not definitely separable from each other; indeed, they often occur side by side, and it would appear that the firmer cheesy matter may become changed through chemical and physical influences into the softer variety. The final outcome of cheesy degeneration is either softening, liquefaction, and absorption, or calcification; but when cheesy material becomes shut off from the surrounding tissues by the formation of a connective-tissue capsule, it often remains for a long time without any special change.

§ 54. **That form of necrosis which terminates in liquefaction of the tissues** (**liquefaction necrosis**) is in so far similar to coagulation

10

necrosis that both are in a measure the **result of infiltration of the dead tissues by liquids.** But while in coagulation necrosis the infiltrated tissues become stiffer, in liquefaction necrosis they break down and liquefy. But not infrequently this liquefaction is either preceded or followed by coagulation. Thus, for example, in coagulation of liquids the formation of the coagulum is very often preceded by the disintegration and solution of the contained cells, and then, on the other hand, the clot itself after a time undergoes liquefaction.

If, as the result of the action of heat upon the skin, the superficial epithelium is killed, and if immediately afterward an exudation of fluid from the neighboring papillary vessels takes place, the epithelium covering the points of the papillæ will become enormously swollen (Fig. 28, *d*). Then at a later stage the protoplasm of the cells will undergo liquefaction, to be followed by a similar breaking down of their membranous envelope, until finally the cells disappear entirely.

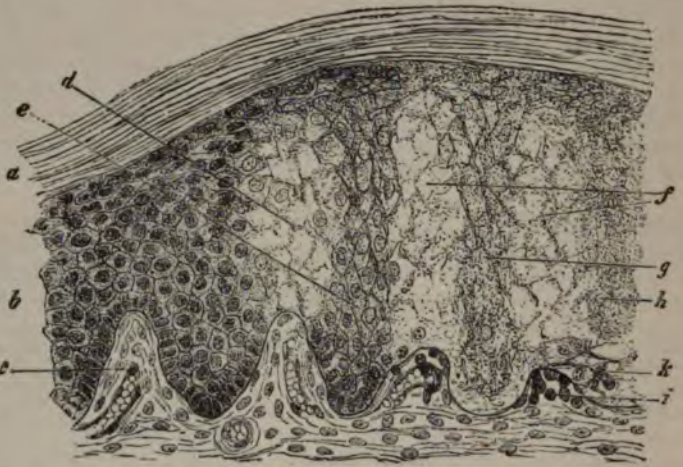


FIG. 28.—Section through the epidermal and papillary portions of a cat's paw, a short time after it had been burned with fluid sealing-wax. *a*, Horny layer of the epidermis; *b*, Rete malpighii; *c*, Normal papilla of the skin; *d*, Swollen epithelial cells, the nuclei of which are still visible at a few points, while at others they have entirely disappeared; *e*, Epithelial cells lying between the papillæ, the upper ones being swollen and elongated, while the lower still remain in a normal condition; *f*, Fibrinous network composed of epithelial cells (broken down so as to be no longer recognizable as such) and exudate; *g*, An interpapillary mass of cells which have become swollen and have lost their nuclei; *h*, A part of a similar mass in which the cells have been entirely destroyed; *i*, A papilla that has been flattened by pressure and that is infiltrated with cells; *k*, Solidified subepithelial exudate. (Carmine preparation. Magnified 150 diameters.)

When a portion of the wall of the stomach is deprived of its circulation by plugging of the vessels, and dies in consequence, a rapid liquefaction of the dead tissue results from the action upon it of the gastric juice.

In anæmic necrosis of the brain the various histological elements of the brain-substance become broken up into smaller and smaller fragments, some of which are absorbed, while others are dissolved in the lymph infiltrating the dead tissue, so that ultimately, in place of the brain-substance, there is a collection of clear, thin liquid. The failure of this liquid to coagulate probably depends upon the small content of the brain-substance in coagulable material, and upon the absence from the lymph of any considerable quantity of fibrinogen. A similar condition is observed in other tissues also, as in the heart, where, in softening of this organ, the muscle-fibres undergo degeneration and disintegration, and are finally completely liquefied in the lymph of the tissues. But in this case there is the difference that coagulation of the muscle-substance at times precedes its solution.

In *inflammations which go on to suppuration* there is invariably a liquefaction of the tissues of greater or less extent, and here it is not only the cells, rich in protoplasm, which succumb, but also the connective-tissue fibres, elastic fibres, nerves, etc.

In inflammations which result in the formation of coagulable exudates and which lead to coagulation necrosis of the inflamed tissue, the coagulated masses as a rule subsequently undergo liquefaction, and, similarly, it is a common occurrence for thrombi to break down and become liquefied.

§ 55. **Necrosis terminating in mummification,** or what is usually called **dry gangrene,** occurs chiefly in parts of the body which are exposed to the air.

Typical examples of dry gangrene are *senile necrosis* of the extremities, more particularly of the toes (Fig. 29) and feet, and *gangrene* of the toes or feet as the result of *freezing*. In the first of these the necrosis is the result of an impaired circulation (cf. § 42, Fig. 19) which is partly dependent upon weakness of the circulation as a whole and partly upon local changes in the blood-vessels. The necrosis which follows freezing is, on the other hand, the direct result of the excessive cooling of the tissues.

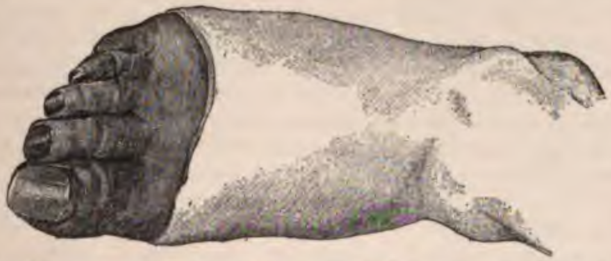


FIG. 29.—Dry gangrene of the toes, caused by narrowing and closure of the arteries which supply these parts—arteriosclerosis.

Since in both the senile gangrene, at the time when the part is actually dead, and in that which results from exposure to cold the tissues are apt to be congested, and since there is diffusion of the blood-pigment throughout them, the affected parts come to have a reddish-black appearance, sometimes spoken of as *black gangrene*. At the same time desiccation occurs, progressing with greater rapidity in cases in which the epidermis has been lost, as occurs frequently in intense congestion and after freezing of a part. The tissues, as the drying progresses, at first become simply leathery, but later they become hard and friable and black. Microscopical examination shows the tissues to be much shrunken and the cells for the most part destroyed.

When an extremity is anæmic at the time of its death, and when for any reason it does not later become penetrated by the blood, it remains pale, and is then said to be in a condition of *white gangrene.*

In the changes which occur in the stump of the umbilical cord in the new-born we have a physiological example of dry gangrene. The gangrenous tissue becomes separated from the neighboring healthy tissue by a zone of inflammation, spoken of as the line of demarcation. Dry gangrene may sometimes develop out of moist gangrene as the result of desiccation.

The terms **moist gangrene** and **sphacelus** are applied to *necrotic tissues which have undergone decomposition and putrefaction.* When the micro-organisms of putrefaction gain access to dead tissues, either directly from the air (as in necrosis of the skin or of the lung) or through the circulation (as may occur in the case of a necrotic testicle or foot), and when the dead tissues are saturated with blood or with lymph, they quickly begin to decompose. An exposed part which is well supplied with blood—the foot, for example—becomes of a dark blue-black color as the result of diffusion through it of the blood-pigment. Bullæ frequently form in the epidermis. When the gangrene is confined to the skin, the gangrenous tissue is warm to the touch, particularly when there is much inflammation in its neighborhood; and hence the name **hot gangrene** has been applied to this variety. When in addition to the skin the deeper tissues are affected, so that the circulation in the dead tissue is quite stopped, the extremity is cool, and there is said to be **cold gangrene or sphacelus.**

Tissues affected with moist gangrene and undergoing decomposition early give off a disagreeable odor and begin to disintegrate. Very trivial mechanical injuries are at times sufficient to cause loss of substance. The tissue is discolored, saturated with bloody liquid, very friable, and at times like tinder. Hand in hand with the changes which have been mentioned above, and which are easily recognizable by the unaided eye, decided chemical changes are going on in the tissues, changes which tend to their ultimate destruction. Under these circumstances gases not infrequently form and give rise to what is called **gangrenous emphysema.** Whether this destruction of the tissue shall progress slowly or rapidly depends chiefly upon the nature of the affected tissue and upon the rapidity of the decomposition going on in it. Bones usually maintain their form for a long time in the midst of a focus of gangrene, while the soft parts disintegrate very rapidly.

The microscope always reveals the presence of bacteria in tissues affected by this lesion (cf. the section on Schizomycetes). The blood-corpuscles disappear early, becoming liquefied or disintegrating into granular masses of blood-pigment. The cells of the tissue become cloudy, lose their nuclei, break down, and become liquefied. Muscle-fibres lose their striations and break up into small homogeneous masses. The medullary sheath of nerve-fibres coagulates into drops. Fat-cells disintegrate, and their contained fat is disseminated throughout the gangrenous mass in the form of small droplets. Connective-tissue fibres swell, become cloudy, lose their sharp contour, and gradually undergo solution. Tendons and cartilage resist for a long time, but eventually succumb to the same changes. In general it may be said that in gangrene there is a gradual solution of the solid elements of the tissues, as the result of which there is formed a dirty-gray, grayish-black, or grayish-yellow, opaque, more or less liquid mass, mixed with remnants of the destroyed tissue. There is, accordingly, a progressive disappearance of all the normal ingredients of the tissue, and a gradual development of formed crystalline elements, the product of the various chemical changes. Thus, for example, there may be found in gangrenous tissue fat-needles, the so-called margarin crystals, fine acicular crystals of tyrosin, globules of leucin, rhombic plates of triple phosphate, black and brown masses of pigment, and crystals of hæmatoidin.

Fig. 30.

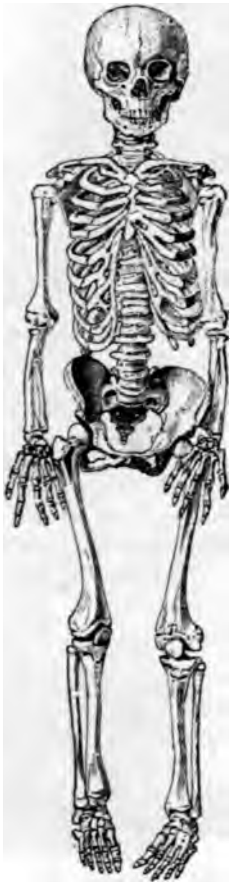


Fig. 31.

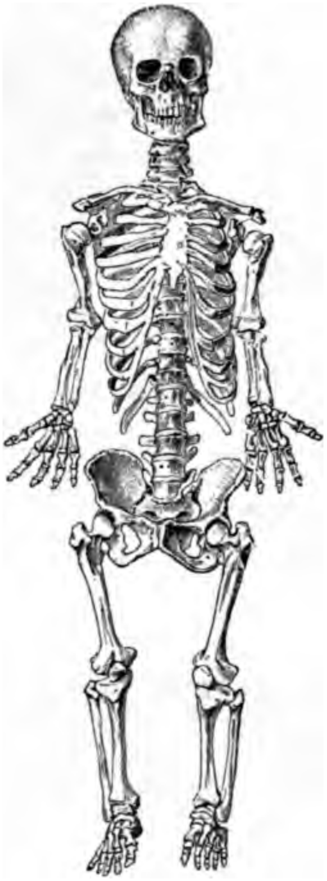


FIG. 30.—Skeleton of a female dwarf, thirty-one years of age, 118 centimetres in height, an idiot, and possessing a klinocephalic skull. All the disks of cartilage at the diaphyses of the long bones and pelvic bones are still present; so also is the frontal suture. The individual parts of the skeleton are, in the main, correctly related to one another, the upper extremities alone being relatively somewhat short.

FIG. 31.—Skeleton of a female dwarf, fifty-eight years of age, 117 centimetres in height, and with a long trunk and very short arm- and leg-bones. The disks of cartilage are still present; the articular ends of the bones are thick.

Moulds may also occasionally develop on gangrenous tissue which is exposed to the air.

Putrefaction, and consequently also gangrene, can only occur through the activity of micro-organisms, and for these a certain content of water is necessary. Accordingly, if the tissues become dry, the development of the germs of putrefaction must cease, or at all events become greatly delayed, and a similar delay in the process of disintegration results. The chemical end-products of the gangrenous destruction of animal tissues are carbohydrates, ammonium sulphide, hydrogen sulphide, valerianic acid, butyric acid, etc., and, finally, carbonic acid, ammonia, and water.

IV. Hypoplasia, Agenesia, and Atrophy.

§ 56. **Hypoplasia,** or defective development, may affect the entire body or only organs or parts of organs, and may occur either during the period of intra-uterine development or after birth, during the period of growth.

When the entire skeleton or a very considerable part of it undergoes maldevelopment, so that the bones are much shorter than normal, abnormally small individuals result, called *dwarfs* (Figs. 30 and 31), whose parts may be either fairly well proportioned (Fig. 30) or else unsymmetrically developed (Fig. 31). In the latter figure may be seen an example of a dwarf whose trunk was of nearly the normal size, while the extremities were abnormally small. Again, the body and extremities may be abnormally small, while the head develops to about the normal size, being then out of all proportion to the body. When the maldevelopment is confined to a single part of the skeleton, or is here much more marked than elsewhere, a rudimentary condition of that part results. Thus, as the result of maldevelopment of the cranium, conditions of *microcephalus* (Fig. 32) and *micrencephalus* (Fig. 33) are induced; as the result of maldevelopment of the humerus or of the bones of the hand we may have shortening of the upper arm or of the hand respectively; and, similarly, maldevelopment of the pelvic bones of one side may lead to asymmetry of the pelvis (Fig. 34).

Fig. 32.

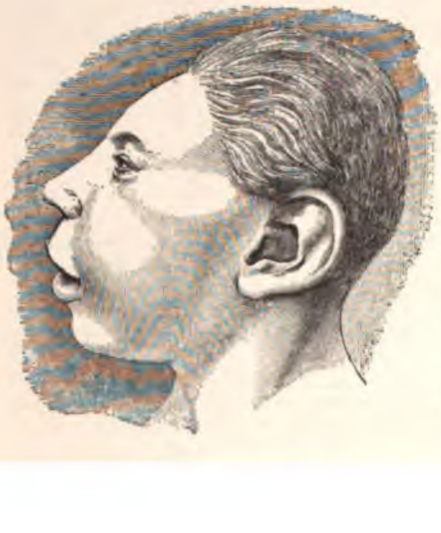


Fig. 33.

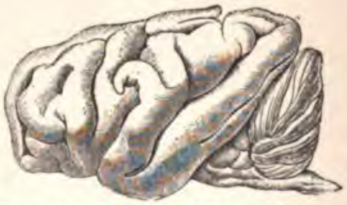


Fig. 32.—Head of Helene Becker (microcephalic), at the age of five years. (From a photograph taken by A. Ecker in 1868.)

Fig. 33.—Brain of Helene Becker (microcephalic), who died at the age of eight years. (From von Bischoff.) This brain weighed 219 grammes (instead of 1377 grammes, as Vierordt claims that it should).

Among the separate organs the central nervous system and the genito-urinary system suffer perhaps most frequently from maldevelopment (Figs. 33 and 35), though the intestine, heart, lungs, and liver by no means escape. In Fig. 33 we have seen an example of abnormal smallness and retarded development of the whole brain; but there are also cases in which one hemisphere alone suffers (Fig. 35), either wholly or in part. A part of the intestine may be so imperfectly developed as to form only a small and quite useless canal (Fig. 37, *d*) or to be merely a small solid cord (Fig. 37, *e*). The uterus not infrequently remains in an undeveloped state (Fig. 36), and occasionally the entire group of female generative organs, both internal and external, may remain at the time of puberty in the undeveloped condition of a young child. Among the organs of the urinary system a more or less complete maldevelopment of the kidney is not uncommon. In the development of the respiratory tract the alveoli of one portion of the lungs may fail to develop, as the result of which a whole lobe or a part of a lobe may be made up entirely of connective tissue and dilated bronchi (Fig. 38).

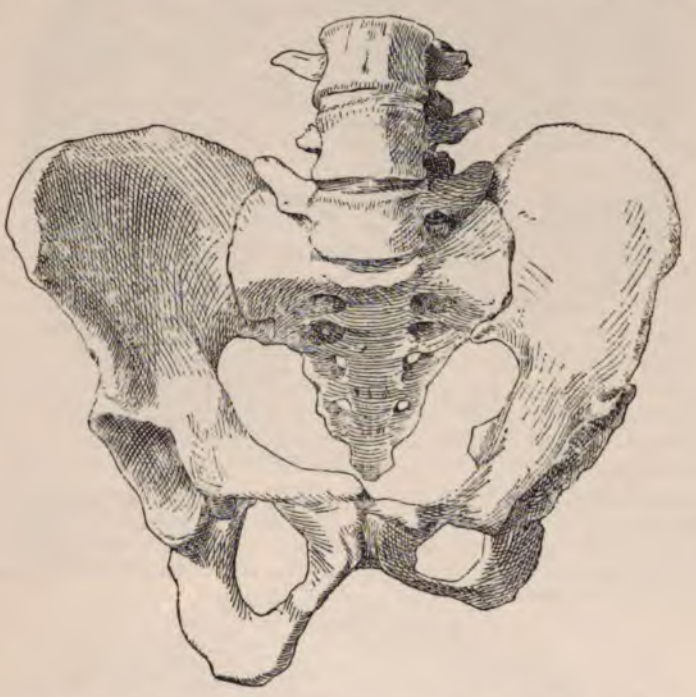


FIG. 34.—Hypoplasia of the os innominatum of the left side, resulting from coxitis which, from the period of childhood, had prevented the use of the left leg. (The reduction in size amounts to a little more than one half.)

The above-mentioned examples of hypoplasia, to which many others might be added, are all due either to causes operating within the developing fœtal organism itself, in which case they may be said to be inherited, or to external deleterious influences working upon normal tissues during their developmental period. Thus, as causes of maldevelopment of the bones, we may mention disease of the thyroid gland (cf. § 22), insufficient

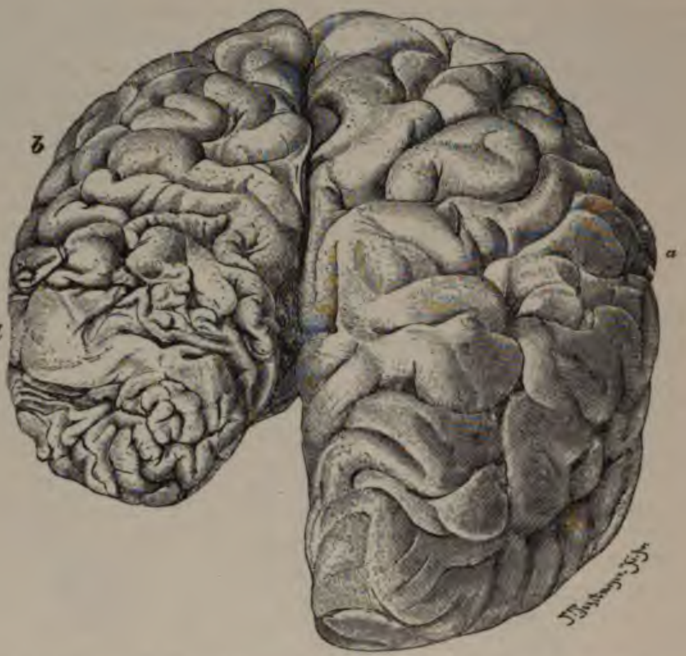


FIG. 35.—Hypoplasia and microgyria of the left cerebral hemisphere; case of a deaf-mute. *a*, Right hemisphere; *b*, left hemisphere; *c*, occipital lobe, diminished in size and in a state of microgyria; *d*, membranous cyst in the region of the parietal lobe. (Seen from above, after removal of the cerebellum. Two-thirds natural size.)

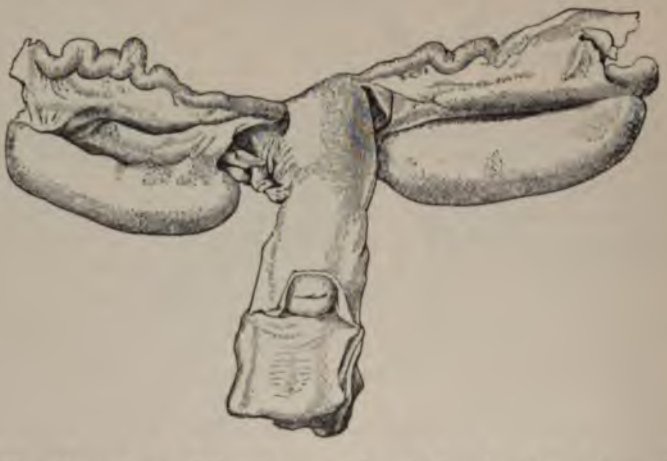


FIG. 36.—Hypoplasia of the uterus, with well-developed ovaries. (From an idiotic girl, eighteen years of age.)

nutrition (rachitis), disuse (Fig. 34), and inflammation. When portions of the body or single organs fail of all development, the condition is spoken of as **agenesia**. This depends upon an entire failure of development of the part in question from the very start, or upon a total destruction of the part after it has begun to develop (cf. the section on Malformations).

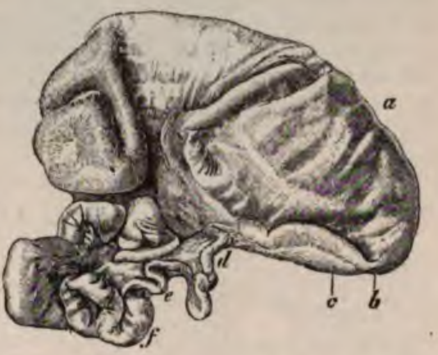


FIG. 37.—Hypoplasia of the small intestine of a new-born child. *a*, A much-dilated portion; *b*, *c*, *d*, *e*, Portions that are much narrowed and wasted; *f*, Normally developed small intestine. (Five-sevenths natural size.)

The tissue composing hypoplastic organs or parts of organs is at times normal in structure; but there is often associated with the abnormal smallness of the organ an *imperfect organization of its integral parts*, with failure of development of some of its more highly specialized elements, so that associated with a hypoplasia of the entire organ there may be *agenesia* of some of its elements. Thus in hypoplasia of the ovary the formation of ova may fail in part; in hypoplasia of the brain there may at the same time be a faulty development of the ganglion-cells and nerve-fibres, and at times portions of the brain may be represented by merely membranous masses (Fig. 35, *d*), in which ganglion-cells are entirely absent; and in hypoplasia of the lung (Fig. 38) there may occasionally be complete failure of development of the alveoli, the lung-tissue then consisting chiefly of rather vascular connective tissue in which bronchi, usually dilated, lie.

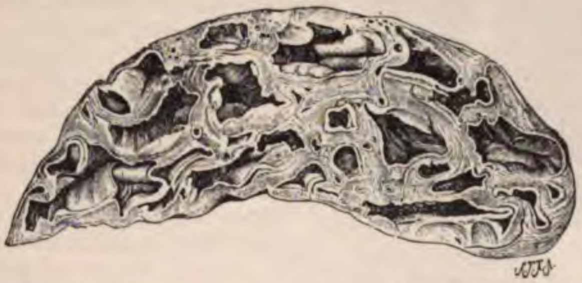


FIG. 38.—Agenesia of the respiratory parenchyma of the left lung. The lung consists of dense connective tissue in the midst of which dilated bronchi are found. (Horizontal section through the apex of the upper lobe. Natural size.)

§ 57. **Atrophy** is diminution in size of an organ as the result of diminution in size and disappearance of its elements. It may occur at any period of life, and is, in fact, a very frequent result of many different pathological processes. Within certain limits it may be regarded as a *physiological process*, since in advanced age a retrograde change in all the organs is of constant occurrence and is always associated with more or less diminution in their size. A few of the organs suffer a similar change even before old age—as, for example, the thymus, which becomes completely atrophied even before the completion of the period of adolescence, and the ovary, a part only of whose ova are discharged during the period of sexual activity, the remainder undergoing atrophy. In the atrophy of old age the lymphadenoid tissues, the muscles, and the bones suffer most as a rule, though there is much difference in this regard in different individuals, the brain or the glands of some of them undergoing the earliest and most rapid change.

The most striking evidence of atrophy of an organ is its diminution in size. When the muscles atrophy (Fig. 39) the affected portions of the body become smaller; and in cases of extensive atrophy of the muscles of the extremities the impression is given as if nothing intervened between the skin and the bones. When the atrophy of an organ goes on symmetrically in all its parts its normal shape may be preserved. But it often progresses more rapidly in one part than in another, in which case great asymmetry of the organ may result, there being often deep pits upon its surface (Fig. 41) and cicatricial contractions (Fig. 44), so that the affected organ—for example, liver or kidney—may present a knobbed or granular surface. In cases in which the tissues undergoing atrophy are in any way prevented from contracting, as is the case in bones and in the lung, the outward form of the organ is preserved. In the case of bone, however, the Haversian canals and the medullary cavity become enlarged, and a condition results which is designated *excentric atrophy* or *osteoporosis* (Fig. 40). In the lungs the alveoli become united into large air-spaces as the result of disappearance of the intervening alveolar walls.

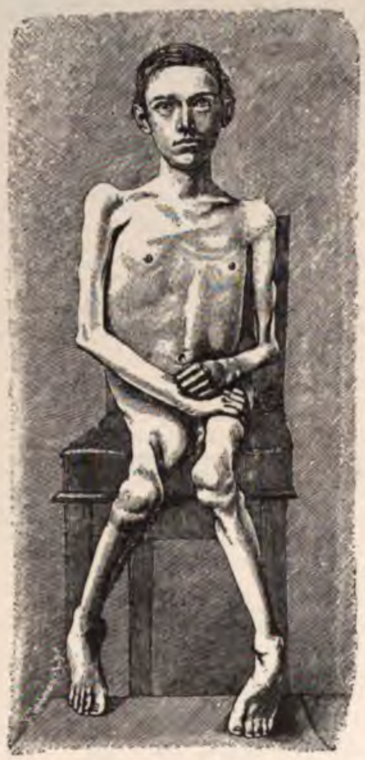


FIG. 39.—Juvenile muscular atrophy. (Case observed by de Souza.)

When atrophy affects glands and muscles there is often a change in their color, though this is of but secondary importance, depending either upon an *unusual distinctness of the pigment* of the affected organ because of the disappearance of parts ordinarily overshadowing it, or upon *the deposit of pigment in the atrophied tissue*, or, finally, upon a changed blood-content of the atrophied tissue.

The diminution in size of atrophic organs is the result of diminution in size and disappearance of the structural elements of the tissues composing them. In the majority of the organs—more particularly glandular organs, muscle, and bone—the more highly specialized portions suffer, in undergoing atrophy, to a much greater extent than the connective-tissue framework which supports them. Indeed, it is not uncommon to find this latter tis-

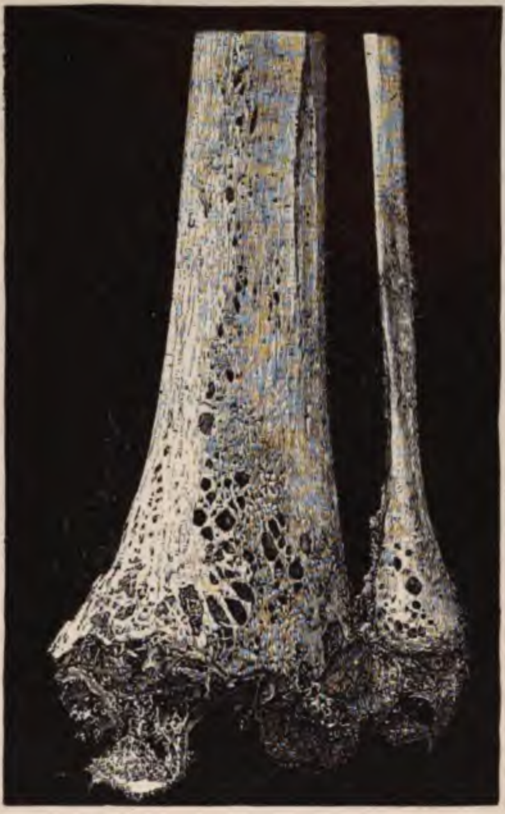


FIG. 40.—Excentric atrophy of the lower ends of the tibia and fibula, with osteoporosis. (Natural size.)

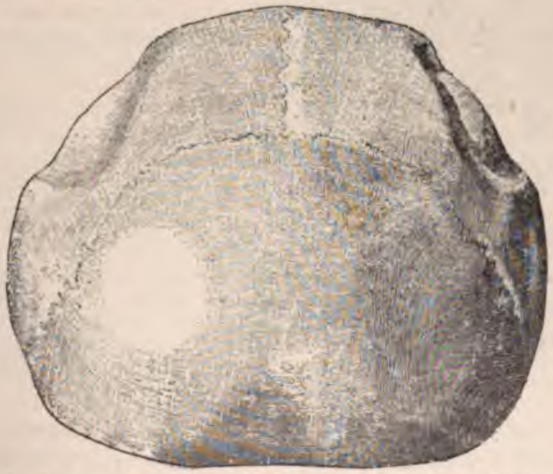


FIG. 41.—Senile atrophy of the calvarium, with defect of the external table and of the spongy portion throughout the central parts of the parietal bones.

sue quite intact, or even increased in amount, in an organ from which all the more highly differentiated parenchyma has disappeared. Thus in atrophic muscle-tissue (Fig. 42) the contractile substance within the sarcolemma frequently disappears entirely without the occurrence of any noticeable atrophy in the connective tissue between the muscle-bundles, the nuclei of which may be actually increased in number (Fig. 42, c_1).

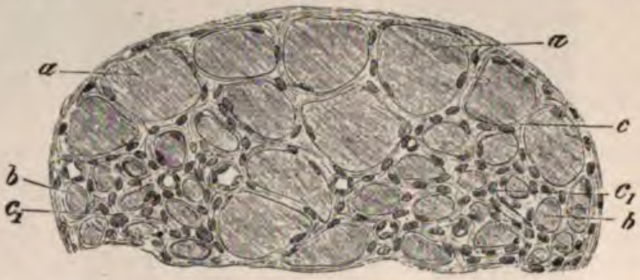


FIG. 42.—Section of an atrophied muscle, from a case of progressive muscular atrophy. *a, a,* Normal muscular fibres; *b,* Atrophic muscular fibres; *c,* Perimysium internum, the nuclei of which, at c_1, seem to be increased in number. (Preparation stained with Bismarck-brown and mounted in Canada balsam. Magnified 200 diameters.)

In atrophy of the kidney the epithelial cells of the urinary tubules (Fig. 43, *f*) become smaller and smaller, and ultimately disappear, the tubules then undergoing complete collapse. A similar change occurs in the epithelium of the glomeruli, the capillaries of which disappear.

The same thing occurs in simple atrophy of the liver, in which the entire parenchyma of a lobe may disappear without any considerable diminution in the amount of its connective-tissue stroma. Similarly the ganglion-cells of the brain and of the spinal cord may atrophy without any diminution in the neuroglia, which is often actually increased in amount.

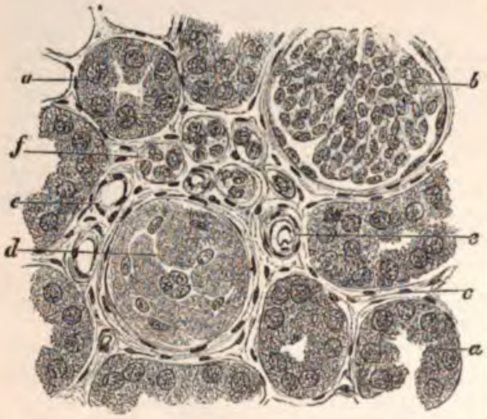


FIG. 43.—Senile atrophy of the kidney. *a, a,* Normal uriniferous tubules; *b,* Normal glomerulus; *c,* Stroma, with blood-vessels; *d,* Atrophic glomerulus; *e,* Small artery, with somewhat thickened intima; *f,* Atrophied and collapsed uriniferous tubules. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 200 diameters.)

In atrophy of bone it is the true bone-tissue which becomes diminished in amount, and in excentric bone-atrophy and osteoporosis the marrow is materially increased. In some cases, however, the fat of the marrow may also disappear, leaving spaces which then become filled with liquid.

In atrophy of lymphatic tissue and of the spleen it is more particularly the free cells which undergo diminution and in parts completely disappear.

The change in an organ resulting in its atrophy may occur without any appreciable change in the structure of its component parts (Fig. 42), the atrophy being the result of a simple diminution in size of the various tissue-elements. This form of atrophy, called **simple atrophy**, is to be carefully distinguished from the **degenerative atrophies**, in which changes in the structure of the various tissue-elements occur from the beginning and are frequently associated with deposits of pathological substances in them. Thus a cell may become granular and undergo fragmentation, or may swell up and liquefy, or droplets of fat or mucus may form in it, all of these changes being indicative of degenerative processes in the protoplasm of the cell. The special *varieties of degenerative changes* which occur in tissues will be treated of in the succeeding paragraphs of this section. Coincidently with changes in the protoplasm of the cell-body there may be similar degenerative changes in the nucleus, such as fragmentation, change of shape, irregular distribution of the chromatin, discharge of the chromatin into the cell-body, and swelling and disappearance of the nucleus, all of which ultimately lead to destruction of the nucleus, and secondarily of the cell itself.

Degenerations thus ultimately leading to atrophy of the affected organ are of very frequent occurrence, particularly in glandular organs. Frequently inflammation is also a complicating factor in the production of these conditions.

Not infrequently **granules** are met with in cells, of such appearance and under such conditions as to preclude the possibility of their being the result of degeneration and disintegration of the cells. These have been made the subject of careful study by Ranvier and Ehrlich. The latter of these investigators has shown the presence in the white blood-corpuscles, under normal conditions, of granules giving distinct reactions with some of the aniline dyes. He is thus able to differentiate cells containing neutrophile granules (which stain with a neutral dye obtained by mixing acid fuchsin and methyl green) and cells containing oxyphile granules (which stain with the acid dye eosin). Under pathological conditions, other leucocytes are also found containing basophile granules, staining with the alkaline dyes.

Besides these cells of the blood, large cells containing basophile granules in large numbers are sometimes found in the connective tissue of various organs, especially in cases in which there is also present a slight but chronic inflammatory process. These cells have been called "**Mastzellen**" (literally "feeding cells") by Ehrlich.

The exact significance of these and similar granules in cells is at present uncertain. Altmann, who by the use of special methods has demonstrated such granules in the greatest variety of cells, sees in them the morphological unit of living matter, and applies to them the name *bioblasts*. Separate, independent bioblasts, such as the micro-organisms, he calls *autoblasts*, while those which are aggregated in cells he calls *cytoblasts*, and these latter he again divides, according to their location in the cell, into *karyoblasts* and *somatoblasts*. This view would appear, however, to be hardly in accord with the facts; and the hypothesis of Ehrlich, in which he is supported by Heidenhain and Löwit, would appear more probable—i.e., that these granules are of the nature of a secretion by the protoplasm of the cells, and that the cells in which they are found may be regarded as in a measure unicellular glands. The investigations of Tettenhamer into the spermatogenesis of salamanders have shown the formation of acidophile granules from degenerating nuclei. Since these find their way into leucocytes as the result of phagocytosis, they may be considered to represent the acidophile formation of granules which takes place in these leucocytes later on. As regards the "Mastzellen," the opinions of different observers are at variance. Some (Browicz, Raudnitz) take them to be degenerating cells; others (Neumann) believe them to be transition stages of proliferating cells; while still others (Ehrlich, Rosenheim, Korybutt-Daszkiewicz) look upon them as being cells which have been superabundantly supplied with food. It certainly militates against this last view that Ballowitz has found the "mast-cells" in hibernating animals, at the end of their winter's sleep, in almost the same number as at the beginning, and that "mast-cells" are often found in persons who have been in a state of cachexia at the time of death.

§ 58. The various **atrophies** may be separated according to their origin into **active** and **passive.** The cause of the first lies in the inability of the cell to assimilate as it should the food which is brought to it. In the passive form insufficient food is brought to the cell, or such as is brought is of an improper kind, or harmful substances are contained in it which impair the nutritive function of the cell. Active atrophy is more particularly observed as a part of *senile degeneration*, but it occurs also under pathological conditions, especially in nerves, glands, and muscles (Fig. 39) whose function is interfered with.

Clinicians are apt to prefer to the above another classification of the atrophies, distinguishing senile atrophy, atrophy dependent upon impaired nutrition, pressure atrophy, atrophy of disuse, and neuropathic atrophy.

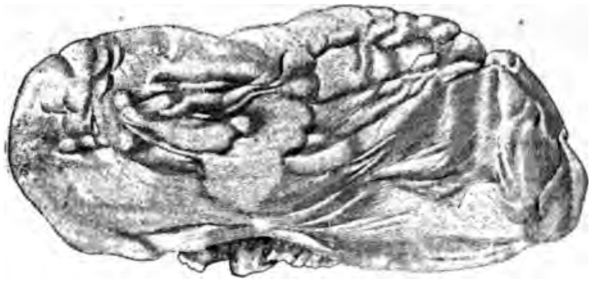


FIG. 44.—Arteriosclerotic atrophy of the kidney. (Natural size.)

Senile atrophy (Fig. 41) is partly active, partly passive, since it is not simply the result of gradually diminishing energy on the part of the cell, but depends also in part upon narrowing and obliteration of the vessels conveying nourishment to it. It may occur in all the organs, and is often more pronounced in one organ than in another. The bones, the kidneys, the liver, the brain, and the heart may all thus suffer a decided diminution in their volume.

The **atrophy dependent upon impaired nutrition** may result from an insufficient supply of food to the body as a whole or from extensive loss of the fluids of the body, and then affects the whole body, although even then the fat, the blood, the muscles, and the abdominal glands suffer most. *Local atrophies* may result from interference with the blood-supply of limited regions (Fig. 44), and are a frequent result of *disease of the blood-vessels.* Furthermore, they are of frequent occurrence as a result of or as a part of *inflammatory processes*, though in this connection it should be stated that the disappearance of the tissue-elements is not, as a rule, the result of simple atrophy, but of a variety of *degenerative changes* which lead to the destruction of the cells and of the tissues.

Occasionally atrophy of a tissue may result from the presence of deleterious substances in the blood. Thus iodine causes in time a diminution in size of the thyroid gland, and in chronic lead-poisoning the extensor muscles of the forearm are apt to undergo atrophy.

Pressure atrophy results from continued and moderate pressure upon a tissue. It would appear to depend both upon direct injury to the tissue and upon interference with its circulation. Typical examples are: the atrophy of the liver which results from tight lacing and consequent pressure of the ribs upon the liver; and the disappearance of bone as the result of pressure of an aneurism (Fig. 45) or of an accumulation of liquid in the ventricles of the brain.

Disuse atrophy occurs in muscles and glands, as well as in bones, skin, and other tissues, and is due to non-use of the tissues in question. In the case of muscles and glands the atrophy is essentially active, but as the result of their functional inactivity there is at the same time a considerable diminution in their nutritive activity and in the activity of the circulation in them. In the other tissues the atrophy is chiefly due to a lowering of the nutrition of the unused parts, though it is impossible to quite eliminate from consideration a change in the power of assimilation of the cells. When the disuse is operative during the developmental period, and the tissue is on that account poorly nourished and undergoes but an imperfect development, the resulting condition is properly regarded as one of hypoplasia (Fig. 34); and yet it is impossible to sharply separate this condition from one of atrophy, since in hypoplasia there may be also a disappearance of structures which had undergone a certain degree of development.

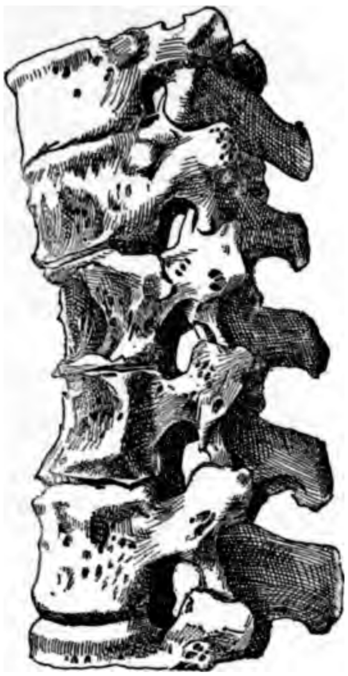
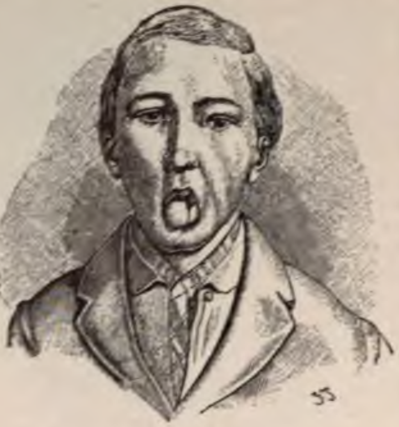


FIG. 45.—Pressure atrophy of the spinal column, caused by the encroachment of an aneurism of the aorta.

Neuropathic atrophy is a result of diseased conditions of the nervous system, and is apparent most often in a rapid atrophy of the nerves and muscles, though it may also affect any of the other tissues.

Thus disease of the anterior horns of the spinal cord or of the motor roots is followed by atrophy of the corresponding nerves and muscles. Injury of the peripheral nerves is commonly followed by atrophy of the skin. As the result of disease of the nerves of one side of the face there may be *unilateral neuropathic atrophy of the face* (Fig. 46). Unilateral affections of the brain during fœtal life or during childhood may lead to atrophy of the opposite half of the body (*congenital and infantile hemiatrophy*).



In all these pathological alterations of neuropathic origin we very often have to deal not with true atrophies, but with various degenerative processes; and the term atrophy as applied to them is only justifiable to this extent, namely, that the ultimate result of the process is an atrophic condition of the affected parts. The causes of the degenerative processes are found in part in vaso-motor disturbances, in part in loss of function, and in part in severance of the affected tissues, the nerves, from their centres in the spinal cord or brain.

FIG. 46.—Facial hemiatrophy. (After Lichtheim and Borel.)

V. Cloudy Swelling and Hydropic Degeneration of Cells.

§ 59. The term **cloudy swelling**, or *parenchymatous degeneration*, or *granular degeneration*, was proposed by Virchow to indicate a condition of swelling and enlargement of cells resulting from absorption of various extraneous substances. He characterized it as a kind of hypertrophy with tendency to degeneration. At all events, the greatest weight is to be laid upon the degenerative character of the change. Histologically the process is characterized by the formation of fine granules within the bodies of the swollen cells—for example, in kidney epithelium, liver-cells (Fig. 47), or heart-muscle. Their microchemical reactions (solubility in acetic acid, insolubility in alkalis and ether) would indicate the albuminous nature of these granules. Their presence gives to the cell a cloudy, granular appearance, and at the same time, as the result of swelling, the normal structure and form of the cell are lost. Thus in cloudy swelling of the tubular epithelium of the kidney (Fig. 48) the rod-like markings of its protoplasm and the cell-processes extending into the lumen of the tubule disappear, the cell becomes larger (*b*, *c*), and dark granules make their appearance throughout its substance. This change is to be regarded as a *disorganization of the cell-protoplasm* following the absorption of liquid into its substance, and leading to a partial separation of its solid and liquid constituents. *The nucleus not infrequently participates in these changes, undergoing a similar disorganization.*

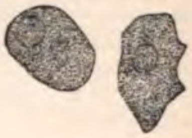


FIG. 47.—Cloudy swelling of liver-cells. (Scraped from the cut surface of the liver of a man who had died of septicæmia; examined in salt solution. Magnified 350 diameters.)

Recovery from a moderate degree of this degeneration is quite possible, in which case the cell is restored to its normal condition; but often there is a complete destruction of the cell, which then ultimately breaks

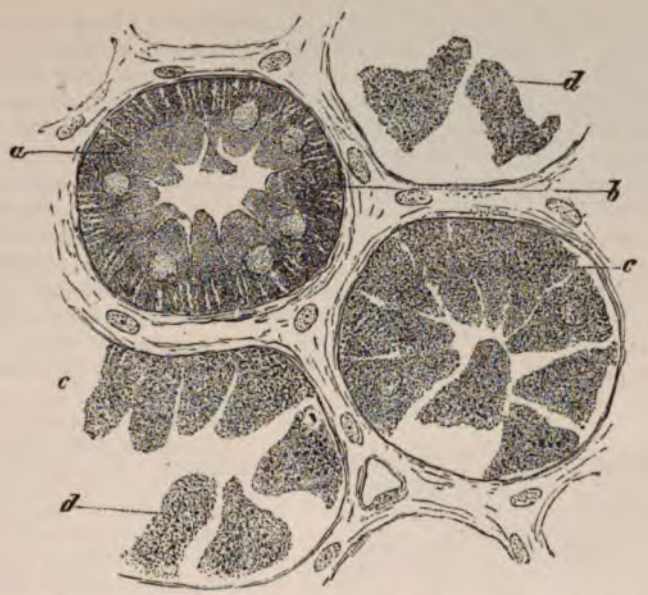


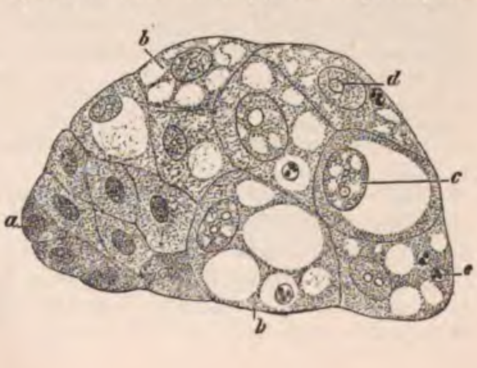
FIG. 48.—Cloudy swelling of kidney epithelium. *a*, Normal epithelium; *b*, Epithelium beginning to be cloudy; *c*, Advanced degeneration; *d*, Cast-off degenerated epithelial cells. (From a preparation which had been treated with ammonium chromate. Magnified 600 diameters.)

up into finely granular fragments. Fatty degeneration (cf. § 62) is frequently associated with the degeneration under discussion.

Cloudy swelling occurs in the cells of nearly all the parenchymatous organs in the course of the majority of the infectious diseases, particularly in scarlatina, typhoid fever, variola, erysipelas, diphtheria, septicæmia, etc. Organs thus affected present a cloudy, less shining appearance than normal, and often appear gray. When the lesion is very marked the tissue has the appearance of having been boiled, its blood-content is generally very small, its consistence is doughy, and the finer details of its structure are lost.

§ 60. The term **hydropic degeneration** is very properly applied to a change frequently observed, in epithelial cells chiefly, whereby they be-

FIG. 49.—Hydropic degeneration of epithelial cells, from a carcinoma of the breast. *a*, Ordinary epithelial cells; *b*, Hydropic cells, with bladder-like drops of fluid (physalides) in their interior; *c*, Hydropic nuclei; *d*, Enlarged nucleoli; *e*, Wandering cells. (The preparation was hardened in Müller's fluid and alcohol, then stained with Bismarck-brown, and finally mounted in Canada balsam. Magnified 300 diameters.)



come swollen as the result of imbibition of liquid. The process is closely related to cloudy swelling, though the resulting disorganization of the cell is usually much less extensive. When epithelial cells undergo this degeneration the cell-contents appear clear, the protoplasm granules being pressed apart by the imbibed liquid, and often being present only as a granular ring at the periphery of the cell; the cells thus coming in a measure to resemble plant-cells (Fig. 49, *b*). Occasionally distinct vacuoles (*b*) are formed—i.e., globular drops of clear liquid in the cell-protoplasm. The nucleus (*c*) also becomes swollen, and may be indicated merely by a large globule with liquid contents. When muscle is the affected tissue, clear droplets of liquid appear between the fibrils, pressing them apart (Fig. 50 and Fig. 51, *a*, *b*), so that, when the disease is extensive, the formation of the clear round spaces may give to the muscle a distinctly bubbly appearance (Fig. 50). For a time the muscle-fibrils between these drops may remain unchanged, but with a continuance of the process they degenerate and undergo *liquefaction*.

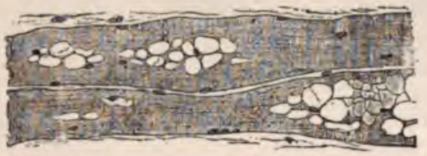


FIG. 50.—Hydropically degenerated muscular fibres, from the gastrocnemius of a patient suffering from chronic œdema of the legs. (The preparation was first treated with Flemming's acid-mixture, then stained with safranine, and finally mounted in Canada balsam. Magnified 45 diameters.)

Hydropic degeneration may be the result of œdema (Figs. 50 and 51), or it may occur in inflammatory conditions or in tumors (Fig. 49). When it results from inflammation its degenerative character is usually much more pronounced than when it occurs merely as an accompaniment of œdema, and it may then lead to complete disintegration of both the cells and the nuclei. In œdematous conditions the cells often remain alive for a very considerable time, notwithstanding their hydropic condition.

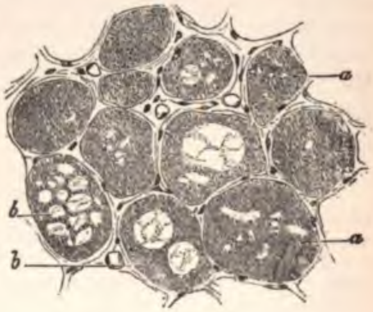


FIG. 51.—Transverse section of a bundle of muscular fibres in a state of hydropic degeneration. *a*, Muscular fibres with small drops of fluid; *b*, Fibres with large drops. (The preparation was hardened in Müller's fluid, then stained with hæmatoxylin, and finally mounted in Canada balsam. Magnified 66 diameters.)

VI. Lipomatosis, Fatty Atrophy, and Fatty Degeneration.

§ 61. Certain of the tissues contain, under normal conditions, a considerable amount of fat, which is present in their cells in such amount as to be readily recognizable to the naked eye. This fat has its origin in the fat ingested with the food, or has been formed in the body from albumin and carbohydrates, and has then been deposited in the tissues in which it is found.

When the ingestion of fat or of fat-forming substances is abnormally great, or the body is unable to make proper use of the fat consumed or elaborated in it, a disturbance of the balance of fat-production and fat-consumption results, leading to an increase of the storing of fat in the body, and in time interfering with the performance of its functions, and thereby assuming pathological importance. This inordinate accumulation of fat leads to the condition termed **obesity**, or *adiposity*, or *lipomatosis universalis*.

The tissues in which fat is normally present are the first to be affected in this process, and consequently the subcutaneous fat-tissue, the fat underlying the serous membranes, the marrow of the bones, and the liver suffer first. Subsequently fat appears in tissues of which it is not a normal constituent, as, for example, in the connective tissue between the muscle-fibres of the heart, in the endocardium of the ventricles and auricles, in the intermuscular connective tissue of the skeletal muscles, etc.

In connective-tissue cells and in the hepatic cells the fat is deposited in the form of small drops (Fig. 52, *a*, *b*), which soon coalesce to form larger drops, ultimately replacing the entire cell-body and converting it into a spheroidal mass of fat.

Obesity may persist as a permanent condition until death, to which it may directly lead at times as the result of interference with the action of the heart. But it may also become less, as the result of diminished ingestion of food or in consequence of improved metabolism, in which case the fat stored up in the cells undergoes diminution, breaks up into smaller drops, and may ultimately be entirely reabsorbed, the cell again assuming the shape and appearance of the connective-tissue cell. Occasionally with the disappearance of the fat there may occur a multiplication of the nuclei of the cell.

When the fat is removed from a tissue normally containing it, in the course of general marasmus, and its place is taken by serum, the tissue assumes a gelatinous appearance, and the resulting condition is spoken of as **serous atrophy of fat-tissue.** When pigment is deposited in atrophic fat-cells, giving to them a yellowish or brownish color, **pigment atrophy** is said to have occurred.

According to Voit, the body may store up fat directly from the fat contained in the ingested food, or it may elaborate it from absorbed fatty acids by a process of synthesis with glycerin, or from albumin and carbohydrates. The important factor in the metabolism of nutrition is not the oxygen of the blood, but the cell itself, whose protoplasm possesses the power to convert complex chemical compounds into simpler ones. The substances most readily lending themselves to this change are the albumin brought to the cell in soluble form and the carbohydrates. Fat is, on the other hand, resistant, both that directly absorbed from the food and that formed in the body. Now, when fat is supplied to the cell in excess, or when the metabolic potential of the cell is lowered so that it is unable to further decompose the fat which it elaborates from the albumin brought to it, fat of necessity remains in its protoplasm. When these two influences act in combination, the effect is, of course, greater. Improved nutritive conditions, exercise, and elevation of the body-temperature increase the metabolic activity of the cells, while it is diminished by alcohol, morphine, and quinine. Obesity depends on assimilation of food in excess of the ability of the body to make use of it. In its production the metabolic power of the cells of the body as a whole may be normal, or it may be diminished as the result of weakness or diminution in number of the cells. The accumulation of fat which is often noticed in anæmia is explained on the ground of diminution in the cell-mass of the body, resulting in diminished metabolic power. The deposit of fat in the intermuscular connective tissue of atrophied muscles would appear to be a direct result of the diminished metabolic changes in the paralyzed muscle-tissue.

According to Gautier the metabolism of proteids in the cell occurs in two stages. In the first, the stage of ferment-action without oxidation, or of hydrolytic separation, uric acid or analogous substances (urates and creatine derivates) are formed from the protoplasm, the carbohydrates at the same time being converted into fats. In the second stage, that of oxidation, the sugars and fats disappear, both those originally derived from the food and those resulting from the metabolism of proteids. The carbohydrates are in part oxidized, but the greater part of them, particularly during muscular inactivity, are converted into fat by a simple fermentative process in the course of which a large amount of carbonic acid is liberated. Ultimately the fats also undergo oxidation and disappear.

§ 62. When a cell contains fat which cannot be accounted for as having been formed from proteids or carbohydrates in the circulation, or as having been obtained from the ingested food, but which would appear to have been formed in the cell at the expense of its own protoplasm, the fat must be regarded as an expression of degeneration of the cell, and the term **fatty degeneration** is applied to the process from which it results.

This degeneration may occur in the course of parenchymatous degeneration as a later development, but it also frequently occurs without any such preceding condition, so that it must be regarded in reality as a splitting up of the protoplasm of the cell with fat-formation.

Cells which are in the condition of fatty degeneration always contain easily recognizable *drops of irregular size*, colorless, highly refracting, insoluble in acetic acid, soluble in alcohol and in ether. Perosmic acid stains these droplets black. Their number and size vary greatly, though the largest rarely attain great size. Thus heart-muscle in a condition of fatty degeneration (Fig. 53) shows minute fat-droplets scattered through its substance, varying in number with the intensity of the process, but which seldom become conglomerated together to form large drops.

Fig. 52.

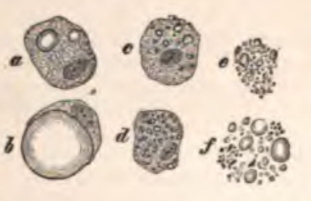


Fig. 53.

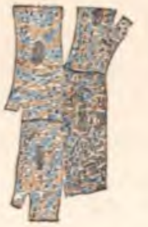


Fig. 52.—Fat-containing liver-cells. *a*, *b*, Fat-infiltration; *c*, *d*, *e*, *f*, Fatty degeneration. (Magnified 400 diameters.)

Fig. 53.—Fatty degeneration of the muscular tissue of the heart. (Magnified 350 diameters.)

A similar appearance is presented by liver-cells (Fig. 52, *c*, *d*) and by the tubular epithelium of the kidney (Fig. 54, *e*, *f*) when undergoing fatty degeneration, though it should be said that here the fat-droplets are frequently of greater irregularity in size, and when the process is far advanced in these organs many of the cells may become broken up into a *fatty detritus* composed of fine granules and minute fat-droplets.

Fatty degeneration affects both connective-tissue cells and epithelium. When many cells closely associated are affected, the condition is usually readily recognizable with the naked eye; the more readily, of course, the more intense the process, the less striking the color of the tissue involved, and the smaller its blood-content. Colorless, transparent tissues, like the intima of the heart and of the vessels, assume an opaque, whitish appearance; the cortical substance of the kidney becomes grayish, and when the process is intense, even yellowish white and opaque; the heart-muscle becomes yellowish, and even the skeletal muscles may come to have a pale yellowish-brown color.

The cells contained in liquids—as, for example, those in pus—frequently undergo extensive fatty degeneration, ending usually in the disintegration of the cell. The same is true of the cells of coagulated exudates.

Fatty degeneration would appear to depend in part upon a change in the composition of the blood, and consequently in the nutritive substance brought to the cells, and in part upon *a lowered vitality of the cells themselves.* An important part in its production is undoubtedly played by *persistent diminution in the supply of oxygen* to the cells (A. Fraenkel), which shows itself, in the first place, by an increased breaking down of albumin and a consequent increase in fat-production, and, in the second place, by the circumstance that it is then no longer possible for the fat so formed to undergo further oxidation.

Since, in this process, the reproduction of albumin does not keep pace with the speed with which it is destroyed, a gradual diminution of the albumin-content of the affected organs must necessarily follow.

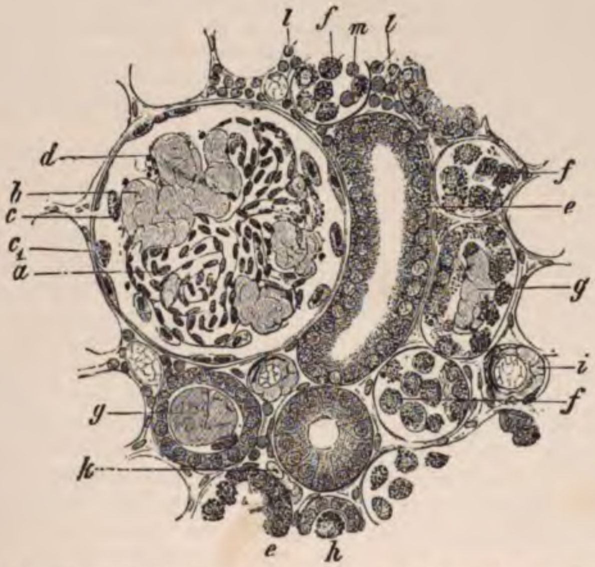


FIG. 54.—Section of a kidney affected with fatty and amyloid degeneration. *a*, Normal loops of vessels; *b*, Loops affected with amyloid degeneration; *c*, Fatty glomerulus epithelium; c_1, Fatty capsule epithelium; *d*, Fat-drops attached to the outer surface of the capillaries; *e*, Fatty epithelium *in situ*; *f*, Cast-off fatty epithelium; *g*, Hyaline solidifications (urinary casts); *h*, Transverse sections of casts composed of fat-drops; *i*, Amyloid artery; *k*, Amyloid capillary; *l*, Cellular infiltration in the connective tissue; *m*, Round cells inside the uriniferous tubules. (Magnified 300 diameters. The preparation was treated with Müller's fluid and perosmic acid, and then stained with methyl violet.)

On this account *fatty degeneration is a frequent accompaniment of conditions producing general or local anæmia.* Thus, if the power of the blood to appropriate oxygen is diminished by disease, as it is in anæmia, leucocythæmia, and coal-gas poisoning, and the processes of nutrition are thereby interfered with, fatty degeneration may occur in a great variety of organs. In cases of serious loss of blood, either from an ulcer of the stomach, or from letting blood too freely from a vein, or from an excessive nose-bleed, it sometimes happens that the patient becomes blind either immediately after the bleeding or perhaps even several days later. In such cases the blindness is to be attributed to fatty degeneration of the cells of the retina and of the optic nerve in the region of the lamina cribrosa, and this degeneration in turn is to be ascribed to the anæmia caused by the hæmorrhage. It is also probable that in these cases the degenerative process is favored by spasm of the arterial vessels of the optic nerve and retina.

Circumscribed areas of fatty degeneration are most apt to occur when a tissue receives an insufficient supply of blood owing to some local lesion, or when the escape of venous blood from the part is retarded, so that renewal of the blood cannot occur at the normal rate. Furthermore, fatty degeneration may occur in cells which have become detached from their normal nutritive surroundings and are undergoing necrotic changes.

Various *poisons* may also bring about increased degeneration of albumin and consequent fatty degeneration. Among such may be mentioned phosphorus, chloroform, iodoform, arsenic, sulphuric acid, nitric acid, and many of the toxic substances produced by the bacteria; and fever would appear to act in a similar manner. In the case of fever it is possible that the degenerative change is in considerable part due to diminished supply of oxygen to the tissue; but the presence of toxic substances in the blood at such times undoubtedly contributes thereto.

The decision as to whether fat which is found in cells is the result of degeneration of the cell-protoplasm, or whether it has merely been deposited in the cell, is not, as a rule, attended with much difficulty. It is generally admitted that the fat resulting from degeneration is in small droplets which rarely become confluent, while the fat deposited in a cell usually runs together to form large drops. While this is true of the fatty changes in most of the organs, it is not universally applicable. It holds for striated muscle, heart-muscle, smooth muscle, neuroglia-cells, etc., but in fatty degeneration of the kidney epithelium the drops which form as the result of the fatty degeneration are already somewhat larger, and in the liver the drops of fat which form as the result of degeneration are both small and large. This is particularly the case in phosphorus-poisoning.

On the other hand, when the fat is merely deposited, and not formed as a result of degeneration, the drops which first appear are small, and then when reabsorption of the fat sets in, the large drops break up into smaller ones.

When the appearance of the fat as it occurs in cells does not afford the necessary indication as to its source, the location of the fatty cells may often serve to determine it. The occurrence of fat-droplets in cells which normally contain no fat, under circumstances excluding the possibility of an increased transport of fat to them, is strong evidence that the fat in question has been formed from the albumin of the cell as the result of a degenerative change. Difficulty arises, then, practically only when the affected tissue is normally a fat-depot and is at the same time prone to fatty degeneration, as is notably the case with the liver; and it is often very difficult to decide how much of the fat present in its cells has been deposited there and how much has been the result of degeneration. A further complication arises from the fact that degeneration-fat may at times be absorbed and then subsequently deposited in the same organ as infiltration-fat.

According to A. Fraenkel, all processes which diminish the supply of oxygen to the tissues in so far tend to increase the waste of proteid substances and prepare the way for fatty degeneration. As the result of the lack of oxygen, he explains, a kind of necrobiosis of the cells occurs. The dead protoplasm is then subjected to the action of various ferments, and by them is split up into a nitrogen-containing substance, which is eliminated in the urine, and a non-nitrogenous substance, fat, which remains in the tissues. Fraenkel bases this theory upon the results of observations in cases of phosphorus-poisoning, in which condition, as has been shown by Storch and Bauer, the consumption of oxygen is materially lowered and the waste of proteids increased; and also upon the results of blood-letting, of hindrance to the respiratory absorption of oxygen, and of carbonic-oxide poisoning, in which conditions fatty-degenerative changes occur, and there is at the same time an increased elimination of nitrogenous substances in the urine. Fraenkel explains the occurrence of fatty degeneration in the course of fever also upon the theory of diminished oxygen-supply, insisting that during the febrile state the oxygen-carrying power of the hæmoglobin is diminished, that the red blood-corpuscles disintegrate in large numbers, and that abnormal contraction of the arteries is present.

The fact that in fatty degeneration the fat remains in the cell-body is explained, according to Voit, not so much by lack of oxygen as by diminished metabolic power of the cells, which are unable to further decompose it.

Tissues which have undergone extensive fatty degeneration, and liquids in which the contained cells have degenerated, very often contain large cells completely filled with fine fat-granules. These cells may properly be called **fat-granule cells.** They are to be regarded as only in part the result of fatty degeneration, and in many cases would appear to be wandering cells which have become increased in size and spheroidal owing to their absorption of fat liberated from other disintegrated cells.

§ 63. The **fats** which occur in the human body are mixtures of *olein, palmitin,* and *stearin.* The first of these is liquid at the ordinary temperature, the second melts at 46° C., stearin at 53° C. Since the fatty portions of various regions of the body contain these fats in different proportions, there is considerable variety as regards their firmness and melting-point. As fat is insoluble in water and aqueous liquids, that contained in the cells of the body or lying free among the tissues is not dissolved by their juices. At most only traces of it can be dissolved in the blood, lymph, chyle, and bile, which contain small quantities of soaps. When the body is cooled after death to a point below the melting-point of the contained fats, the palmitin and stearin separate in the form of fine star-shaped or feathery needles (Fig. 55, *b*, *c*, *d*), which are commonly called **margarin crystals,** and which are often found both in fat-cells and free in the tissue-liquids.

Cholesterin in the form of thin rhombic plates, often with irregular corners and edges (Fig. 55, *a*), is frequently deposited in areas of fat-containing detritus which may have originated from extravasated blood or from degenerated masses of cells. This may occur, for example, in the tunica vaginalis testis, in a dilated sebaceous duct or gland, or in a softened of the intima of a diseased aorta. When the substance in which these cholesterin plates form is liquid, they may often be visible to the naked eye as little glistening scales.

Cholesterin is a constant ingredient of the bile, in which the bile salts and soaps hold it in solution. It occurs also in the medullary sheath of nerve-fibres, and in small amount in the blood, where it is similarly held in solution by the fats and soaps. Burchard believes it to be present in small amount in all the organs.

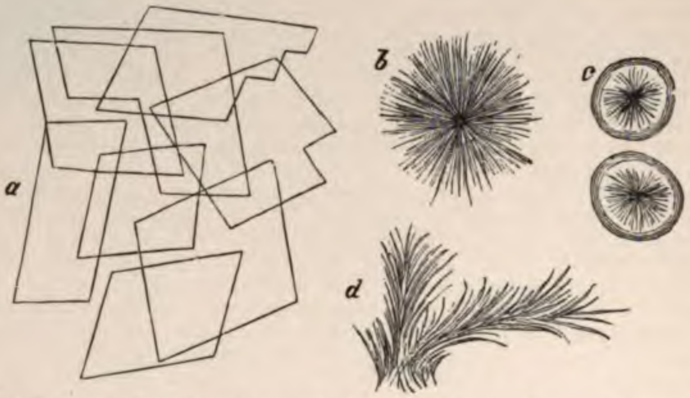


FIG. 55.—*a*, Cholesterin plates; *b*, A free cluster of margarin needles; *c*, Needles inclosed in fat-cells; *d*, Grass-like bundle of margarin needles. (Magnified 300 diameters.)

Water, dilute acids, caustic alkalis, and cold alcohol fail to dissolve cholesterin, which is, however, soluble in boiling alcohol, ether, chloroform, and benzol.

When treated with a mixture of 5 parts concentrated sulphuric acid and 1 part water, cholesterin crystals assume a deep carmine-red color, beginning at their borders, and this color then slowly changes into violet. A weaker solution (3 parts sulphuric acid, 1 part water) causes a violet coloration of the edges of the crystals. Sulphuric acid containing a trace of iodine colors the crystals violet, blue, green, and red.

The source of cholesterin is not clearly understood. It is, however, in all probability an intermediate product in the metabolism of proteids. Pathologically it is met with more particularly when these bodies are undergoing degeneration with fat-formation, or, in other words, in tissues and exudates which are in process of fatty degeneration. It is also occasionally formed in old echinococcus cysts.

VII. Glycogen-deposit in the Tissues under Pathological Conditions.

§ 64. **Glycogen** is a carbohydrate, readily convertible into sugar, which is obtained chiefly from the carbohydrates of the food, but which may also be formed from albumin and from gelatin.

Glycogen is found in the tissues as a *hyaline substance* somewhat resembling amyloid in appearance (Langhans). It is more often situated in the cell-bodies, but may also lie at times in the intercellular spaces of the tissue, and it is generally in the form of spherules of different sizes. In the cells these spherules usually lie rather near the nucleus.

Although glycogen is soluble in water, there would appear to be, according to Langhans, some difference in the degree of its solubility when obtained from different tissues, that contained in the liver, kidney, muscles, pus-corpuscles, etc., being distinctly more easily soluble than that from cartilage-cells and pavement epithelium. Hardening of tissues in alcohol makes the contained glycogen distinctly less soluble. The glycogen contained in the liver at the time of death is quickly converted into sugar by the diastatic ferment of the liver.

Iodine causes glycogen to assume a brownish-red color. To avoid the solution in water of the glycogen contained in fresh preparations, it is advisable to immerse the portions of tissue for examination in a syrupy mixture of gum and iodine (Ehrlich), or in glycerin to which a little iodine has been added (Barfurth). Sections of tissues which have been hardened in alcohol may be best studied after treatment with a dilute iodine tincture (1 part tincture of iodine, 4 parts absolute alcohol) and clearing in oil of origanum. The reaction after such treatment is of considerable duration.

Glycogen occurs normally in the liver, in the muscles (including the heart-muscle), in the leucocytes, in the blood-serum (Gabritschewski), in cartilage-cells, and in almost all embryonic tissues, as well as in the fœtal membranes of young embryos. During starvation the glycogen of the liver undergoes diminution, and under pathological conditions it may disappear entirely.

In diabetes there is a deposit of glycogen in the epithelium of the kidney, particularly in that lining Henle's loops, in the isthmus of which the cells are commonly almost filled with it, leaving, after solution in water, clear spaces in the cell-bodies. The glycogen in the blood is also much increased in diabetes—both that within the corpuscles and that in the blood-plasma (Gabritschewski).

In fresh inflammatory exudates glycogen may be present in the pus-cells. The leucocytes of the blood contain glycogen in excess, more particularly in conditions of cachexia (Czerny). Glycogen has also been observed in tumors of various kinds, as, for example, in the epithelial cells of condylomata, in carcinomata and adenomata of the testicle, in endotheliomata (Driessen), in myxosarcomata, enchondromata, sarcomata of bone, and more rarely, also, in those of other tissues. It is almost never found in tumors of the breast (Langhans), and it is very unusual to meet with it in carcinomata of the stomach or intestine, in tumors of the ovary, of the kidney, and of lymph-nodes. It is also absent from fibromata, lipomata, myxomata, osteomata, angiomata, leiomyomata, and from the tissue of the infectious granulomata (Langhans).

According to Langhans, glycogen is met with in the epithelium of the body and portio vaginalis of the uterus, but is absent from the tubes and is very scanty in the cervix. It is also present in the epithelium of the vagina and in tumors of the portio vaginalis and of the vagina, which contain stratified epithelium. Carcinomata of the uterus rarely contain more than minute traces of glycogen.

VIII. Mucous and Colloid Degenerations.

§ 65. **Mucous degeneration** has its physiological prototype in the production of mucus by the mucous membranes and mucous glands, and in the formation of mucus in the connective tissue of the umbilical cord, of tendons, of bursæ, and of synovial membranes. In the umbilical cord the mucus occurs as a jelly-like matrix; in the joints, bursæ, and tendon-sheaths it forms a stringy, clear liquid.

The formation of mucus in mucous membranes takes place in *epithelial cells*, called beaker- or goblet-cells, whose cell-bodies are in great part occupied by clear substance, the mucus which has been elaborated at the expense of their protoplasm. In mucus-formation in mucous glands the epithelial cells swell, their centres become transparent, and the protoplasm granules become reduced to small groups or strings. The so-called mucus-corpuscles of the salivary secretion, characterized by glassy transparent contents in which vibrating protoplasm granules are often present, are spheroidal cells which have undergone mucous degeneration.

The mucus thus formed from the protoplasm of the cells may be discharged, and the cell may either retain its integrity or it may be completely destroyed.

The formation of mucus occurs under pathological conditions in the same manner as normally. In catarrh of the mucous membranes (cf. Section VI.) the stringy excretion which forms is chiefly the result of excessive mucus-production by the cells of the mucous membrane and of its glands. Pus-corpuscles may also undergo mucous degeneration, in the course of which mucin would appear to be formed from the nuclein of their nuclei (Kossel). In mucous membranes containing cylindrical epithelium the number of beaker-cells is greatly increased as the result of catarrhal inflammation, and the exudate often contains cells which have undergone complete mucous degeneration, and which appear as glassy masses often containing a few fine granules. Again, the cells may contain mucus in the shape of irregular drops of various sizes.

Just as in normal tissues, so also in pathological, the epithelial cells may undergo mucous degeneration. Thus the epithelial lining of cysts of the ovary and of tumors of the intestine may often contain many

Fig. 56.

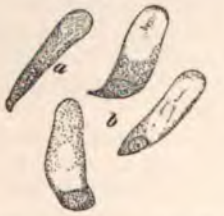


Fig. 57.

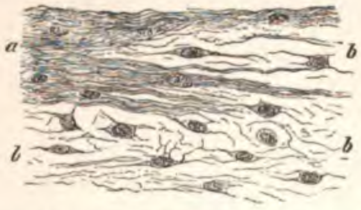


Fig. 56.—Epithelial cells which have undergone mucous degeneration, from a cystadenoma of the ovary. *a*, Cells which are only slightly affected; *b*, Cells which show a high degree of mucous degeneration. (Magnified 400 diameters.)

Fig. 57.—Mucous degeneration of the connective tissue of the aortic valves. *a*, Fibrous tissue; *b*, Tissue that has undergone mucous degeneration. (The section was made from a frozen specimen that had been treated with osmic acid; it was then mounted in glycerin. Magnified 350 diameters.)

beaker-cells (Fig. 56, *a*) and cells in which the entire cell-bodies have changed into mucus (Fig. 56, *b*). In some carcinomata a large part of the epithelial cells undergo a mucous metamorphosis.

A number of the *connective-tissue group of tissues* may also undergo a form of mucous degeneration, and in consequence acquire a gelatinous, transparent appearance. Besides connective tissue itself, cartilage, bone, fat, bone-marrow, and the tissue of sarcomata may be mentioned as belonging to this class. It is here more particularly the intercellular matrix (Fig. 57, *b*) which undergoes the mucous change, becoming converted into a homogeneous, structureless mass. The cells themselves may remain unchanged, may become fatty, or may also undergo mucous degeneration, in which case the whole tissue becomes a clear translucent mass, with scarcely anything left to suggest the original tissue, except here and there connective-tissue bands and single cells or groups of cells less degenerated.

The stringy, gelatinous material which results from mucous degeneration is no single chemical substance, since in it several different varieties of mucin and pseudomucin may be detected.

The **mucins**—of which several kinds may be distinguished, according to their source, as submaxillary mucin, intestinal mucin, tendon mucin—are nitrogenous substances, which dissolve or swell up in water, forming a stringy, mucous liquid. From such solution they are precipitated by acetic acid in the form of stringy masses which fail to redissolve in excess of the acid, thus differing from the true albuminoids. They dissolve in neutral salt-solutions and in caustic alkalis and alkaline carbonates, gradually forming alkali albuminates in the latter. All mucins contain both nitrogen and sulphur, the percentage of carbon, oxygen, nitrogen, and sulphur varying somewhat in the different varieties.

By proper treatment a carbohydrate, called animal gum (Landwehr, Hammarsten), may be separated from the mucins; and mucin may therefore appropriately be called a glycoproteid (Pfannenstiel).

Pseudomucin is also soluble in water, appearing then as a mucous liquid, from which alcohol throws it down in the form of stringy flakes, which are again soluble in water. Acetic acid does not precipitate it. On boiling with dilute mineral acids a carbohydrate is formed (as was the case with mucin) which reduces copper sulphate in alkaline solution (Pfannenstiel).

According to Pfannenstiel, pseudomucin occurs in the proliferating glandular ovarian cystadenomata, and to a certain extent also in the papillary ovarian cystadenomata, and the peculiar gelatinous and mucous consistence of the contents of these cysts is due to its presence. It is produced by the epithelium of these tumors (Fig. 56), and in forming this material these cells undergo changes analogous to those described in discussing the formation of mucin by epithelial cells. In all probability the gelatinous substance found in colloid cylindrical-cell carcinomata is a substance closely related to pseudomucin or metalbumin—i.e., there are several varieties of pseudomucin, of which the two mentioned are examples.

The mucin-like substance contained in the *synovial secretion*, coagulated by acetic acid, differs, according to Salkowski, from nucleo-albumin in that it contains no phosphorus, and from ordinary mucin in its different conduct with the mineral acids, since it is not converted by them on boiling into a reducing substance.

In the blood, in the bone-marrow, in the spleen in leucæmia, and in excretions from the inflamed bronchi in bronchial asthma, sharp, slender, colorless octahedral crystals are not infrequently found. They are called, after their discoverers, *Charcot's crystals* or *Leyden's crystals*.

Salkowski believes these to be composed of a substance closely related to mucin, but crystalline in form. Schreiner, on the other hand, declares them to be composed of the phosphate of a base newly investigated by him, which he describes as a decomposition product of albumin and perhaps nearly related to the ptomaïnes. Curschmann believes these crystals to be formed from disintegrating blood-corpuscles, and Ungar has been able to produce them artificially by allowing sputum to stand in a moist chamber.

§ 66. **Colloid degeneration** is closely related to mucous degeneration, in that it too is the result of degenerative change in an albuminoid body, namely, the protoplasm of the cell. Nothing is known with certainty as to its chemical nature. It is certainly formed from the protoplasm of the cell, and occurs physiologically (in extra-uterine life) in moderate degree in the thyroid gland. Here, at this period, it is found lying in the midst of the parenchyma of the gland (Fig. 58, *c*), in the form of variously sized spherules, which are somewhat crowded together, and which, on section, present a translucent appearance suggesting boiled sago or lard. They are usually of a yellowish or brownish color, and of the consistence of firm jelly.

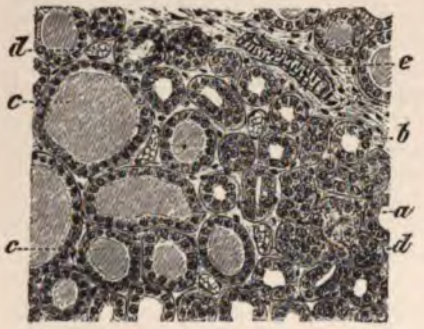


FIG. 58.—Colloid in a specimen taken from an enlarged thyroid gland. *a*, Follicle filled with cells; *b*, Follicle with a lumen; *c*, *c*, Masses of colloid; *d*, Capillaries; *e*, Connective-tissue septum, with artery. (Specimen stained with alum hæmatoxylin. Magnified 60 diameters.)

When this colloid is pathologically increased in amount it may come to compose by far the greater part of the whole volume of the thyroid gland, and may cause it to be greatly enlarged (colloid goître).

Microscopically the colloid of the thyroid gland possesses a homogeneous appearance; it contains but very few cellular elements, and these confined to the periphery of the mass, where the colloid is in process of formation. Occasionally a large mass will be made up of a number of smaller ones, or may be mottled with vacuoles. In the formation of colloid, small, homogeneous, spheroidal masses first make their appearance in the cells of the thyroid, and these, as they continue to grow, may be discharged from the cell or may gather together into a single mass filling the entire cell-body. As far as can be judged from a histological examination, colloid may also develop from masses of desquamated epithelial cells (Fig. 59, *g*), in which case the individual cells break down and form a single homogeneous mass.

Colloid masses, in all particulars similar to those above described, are occasionally contained in the renal tubules of diseased kidneys (Fig. 59, *f*, *h*), and often in the follicles of the hypophysis cerebri (the pituitary body). In the tubules of kidneys which have undergone cystic degeneration such colloid spherules are sometimes present in large numbers. Occasionally the connective tissue of the diseased and atrophied gastric mucous membrane may contain hyaline bodies similar to colloid.

Colloid is distinguishable from mucus in that it does not swell or dissolve in water, that acetic acid does not coagulate it, and that it is not made opaque by the action of alcohol or of chromic acid.

Observations by Biondi, Langendorf, Podbelsky, and Hürthle would indicate that a part of the colloid substance produced in the follicles of the thyroid gland finds its way into the lymphatics; for at the points where these vessels come in contact with the glandular tissue, a melting-down of the epithelium takes place, and an opening is established between the sacs which contain this broken-down material and the lymphatic channels.

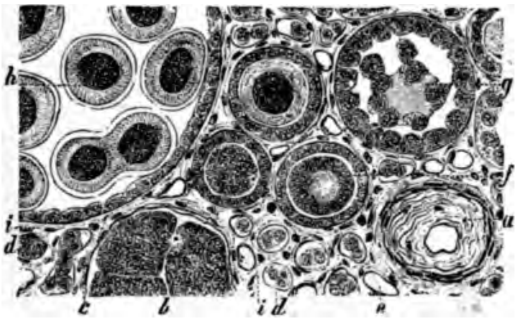


FIG. 59.—Section of a contracted kidney, showing arteriosclerosis and masses of colloid in the uriniferous tubules. *a*, Thickened artery; *b*, Wasted glomerulus; *c*, Capsule of the glomerulus; *d*, *e*, Atrophic uriniferous tubules; *f*, Tubules with laminated colloid casts in their interior; *g*, A hyaline mass with epithelial cells imprisoned in its substance; *h*, Cysts containing laminated colloid spheres; *i*, Stroma. (Preparation stained with alum carmine and mounted in Canada balsam. Magnified 150 diameters.)

Von Recklinghausen, in his work on the general pathology of nutrition, unites, under the heading *colloid degeneration*, several different degenerative processes, particularly what we now know as amyloid, mucous, and hyaline degenerations. He believes that amyloid, as well as mucin and hyaline, is formed from the cell-protoplasm, and that it possesses, in common with the other two, the quality of insolubility in the liquids of the body, at most simply swelling in them; or, in other words, that it possesses in a high degree the qualities of the so-called colloid substances (Graham). Hyaline substance, in particular, he describes as a proteid, staining deeply with eosin, carmine and picrocarmine and with acid fuchsin, homogeneous and highly refractive, little acted upon by acids, and very similar to amyloid substance in its resistance to the action of alcohol, water, ammonia, and acids, though differing from it in giving no reaction with iodine. In its formation there is usually fusion of the cell-substance of adjacent cells.

According to von Recklinghausen, hyaline substance occurs:

1. In cysts of the thyroid gland, of the hypophysis, of the mucous glands, and of the accessory glands of the female generative organs and of the urinary tract.
2. In the eye, as knob-like prominences on the hyaloid and vitreous membranes, or as membranous deposits and thickenings upon them, and in the semicircular canals of the ear.
3. In glandular organs which are in a condition of acute or chronic inflammation, especially in the renal tubules, in the form of hyaline casts, also in the ducts of the sweat-glands and in the follicles of the ovary.
4. In hyperplastic tumors of connective and lymphatic tissues, in lymphomata, tubercles, sarcomata, myxomata, in the choroid plexus, in colloid milia of the skin, in lymphangiomata, and in carcinomata; occurring in these in the form of globular or irregular masses, and sometimes in that of membranes and tubes.
5. On the surface and in the superficial layers of mucous membranes as an important component of diphtheritic false membranes.

6. As deposits on the endocardium and on the walls of the larger blood-vessels and in the capillaries (hyaline thrombi), as well as in the form of hyaline deposits in the walls of the vessels.

7. As a wax-like degeneration of muscle, as a deposit in the axis-cylinders of nerves, and as Morgagni's spheres (*Morgagni'sche Kugeln*) in cataractous lenses.

What von Recklinghausen thus describes under the term hyaline has heretofore been classed in part as colloid degeneration, in part as the result of coagulation necrosis, in part as thrombosis, and in part as hyaline degeneration of connective tissue, and I cannot yet bring myself to accept von Recklinghausen's view, as he appears to me to class together, under the name hyaline, substances which would seem to be quite different. Thus what he classes under 5 and 6 as hyaline is for the most part nothing but more or less homogeneous fibrin, while that which is grouped in class 1 must be regarded as colloid. The fibrin is a product of the plasma of blood-plaques and of leucocytes; colloid is a product of epithelium.

Furthermore, the reactions described by von Recklinghausen as characteristic of hyaline seem to me to be altogether insufficient. All the dyes mentioned stain many entirely different substances very intensely, and fibrin coagulated in homogeneous masses, and cells which are massed together, are often very resistant to alcohol, water, and dilute acids.

IX. Amyloid Degeneration and Amyloid Concretions.

§ 67. The term **amyloid degeneration** is applied to a *peculiar degenerative process of a number of tissues and organs, in the course of which an albuminous material called amyloid substance is deposited in the affected parts*, causing them to increase in size and to assume a *peculiar waxy appearance*. It may occur in almost all the organs of the body, but is more frequently met with in the spleen, liver, kidneys, intestine, stomach, suprarenal bodies, pancreas, and in the lymph-glands. It is encountered less often in fat-tissue, in the thyroid gland, in the aorta, in the heart, in the muscles, in the ovaries, and in the uterus.

When extensive it is readily recognizable by the naked eye, as the affected parts present a translucent waxy appearance (*lardaceous degeneration*).

In the spleen the change occurs most frequently in the region of the glomeruli, which may become completely changed into homogeneous, transparent areas resembling grains of boiled sago, whence this form of amyloid spleen has come to be called the *sago-spleen*. When the amyloid degeneration is present also in the spleen-pulp, more or less distinctly recognizable waxy lines and streaks appear on its cut surface. At times almost the entire substance of the spleen may be thus affected. The spleen is then enlarged and feels hard, and may look as if composed entirely of wax (*lardaceous spleen*).

The changes in the appearance of the liver are similar in that here also, when the amyloid change is extensive, clear, translucent waxy areas appear, which may subsequently become confluent and lead to a considerable enlargement and hardening of the liver. The liver-tissue lying between the masses of amyloid substance may be redder than normal, or it may look pale and yellowish because of fatty degeneration in it.

The kidney may also be increased in size and in firmness of texture as the result of amyloid degeneration, and may, at times, in spots or throughout its whole substance, present a similar waxy appearance. In other cases the waxy areas may be so small as to be invisible to the naked eye, and it may be only through the presence of other visible changes, especially of fatty degeneration, that one is led to suspect amyloid. In the intestine, also, the amyloid is rarely distinguishable without optical and chemical aids, and the same holds true of most of the organs in which amyloid is of rarer occurrence, as in fat-tissue, in the heart, in the larger arteries, the thyroid gland, etc.

The substance which is deposited in amyloid degeneration forms for the most part *shining, homogeneous masses* which develop a *peculiar reaction with iodine and with some of the aniline dyes.* Iodine in water, or, better, in a solution of potassium iodide, when poured over amyloid tissue, causes the amyloid substance to assume a dark mahogany-red color. In thin sections, under the microscope, this reaction differentiates the amyloid substance very clearly from the pale-yellow surrounding tissue (Fig. 60, *b*).

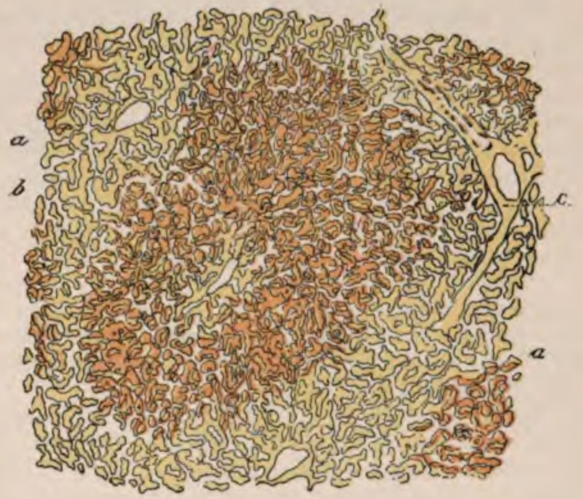
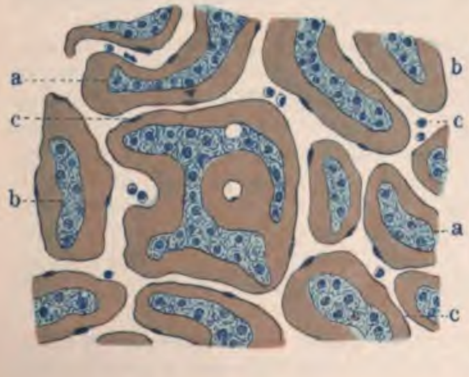


FIG. 60.—Section of an amyloid liver, showing the effects of staining it with a solution of iodine. *a*, Normal liver-tissue; *b*, Tissue that has undergone amyloid degeneration; *c*, Glisson's capsule. (Magnified 35 diameters.)

In very well-marked amyloid degeneration, when the tissues are of an almost wooden hardness, this reaction sometimes results in the production of a violet or bluish or green color; and specimens which have been changed to a mahogany color by the action of iodine, when treated with dilute sulphuric acid or with solution of chloride of zinc, may similarly turn red, violet, blue, or green, or, on the other hand, the original mahogany color may simply be intensified. This reaction is, however, often unsatisfactory.



The aniline dye known as methyl violet or aniline violet colors amyloid substance ruby red (Fig. 61, *b*), while the healthy tissue is at the same time stained blue or deep violet (Fig. 61, *a*, *c*, *e*).

FIG. 61.—Section of an amyloid liver after being treated with methyl violet and acetic acid. *a*, Elongated masses of liver-cells; *b*, Amyloid substance; *c*, Endothelium of the capillaries; *e*, Colorless blood-corpuscles. (Magnified 150 diameters.)

Virchow, the discoverer of amyloid substance, was the first to observe its peculiar reaction with iodine, from which he inferred that amyloid must be devoid of nitrogen and must be nearly related to cellulose or starch, since cellulose, when treated with iodine and concentrated sulphuric acid, assumes an intense blue color, and similarly starch becomes of an ultramarine blue when treated with iodine alone. Virchow accordingly gave the name amyloid to the newly discovered substance. It was not until several years later that Friedreich and Kekulé demonstrated that the so-called amyloid is in reality a nitrogenous substance of an albuminous nature.

The peculiar reaction of amyloid substance makes it possible to detect its presence in the tissues in cases in which it is present in such small amount as to be quite invisible without the aid of iodine. In applying the test to fresh tissues, care should be taken to wash out the blood as perfectly as possible, since the color resulting from the combination of the red hæmoglobin and the yellowish-brown iodine rather closely resembles the mahogany red of the amyloid.

Amyloid is very resistant to acids and alkalis. It is not changed by alcohol and chromic acid, and it is only slowly affected by the changes of putrefaction.

Amyloid material is deposited *in the framework composed of blood-vessels and connective tissue, and more particularly in the walls themselves of the smaller blood-vessels.* Living cells are not affected by it. In connective tissue the amyloid material would appear to be first deposited between the connective-tissue fibres.

In the acini of the liver the amyloid material is found in close proximity to the capillary tubes. The endothelium (Fig. 61, *c*) is covered on its outer side by a more or less thick layer of homogeneous, glassy substance composed wholly of amyloid material. The liver-cells between the amyloid masses are either well preserved (Fig. 61, *a*) or they may be compressed and already undergoing atrophy. They often contain fat. The larger blood-vessels of the liver also at times show amyloid changes, more particularly in the media of the arteries.

In the kidney (Fig. 62) the amyloid is found most abundantly in the walls of the vessels, the vessels of the glomeruli (Fig. 62, *b*) being moderately swollen and homogeneous, and similar homogeneous deposits occurring also in the arteries (Fig. 62, *i*), veins, and capillaries (Fig. 62, *k*) of other parts of the kidney. In the mucous membrane of the intestine the amyloid deposit also occurs in the walls of the blood-vessels more particularly.

In fat-tissue, which is often extensively affected with amyloid disease, the waxy material is found both in the walls of the blood-vessels and in the connective-tissue stroma, so that at times the thin connective-tissue sheath of the fat-cells may be converted into a clear hyaline substance. In lymph-glands and in the spleen, as has been already said, it is the connective-tissue framework which is more especially affected and which often becomes much thickened (Fig. 63, *a*, *b*). In striated muscle it is the perimysium internum and the sarcolemma which are involved. In glandular organs possessing a tunica propria—as, for example, the mucous glands and the kidney—this membrane may also be affected and swell to a very considerable extent.

The **results** of amyloid degeneration which make themselves apparent to the eye, and which in a measure account for the perversions of

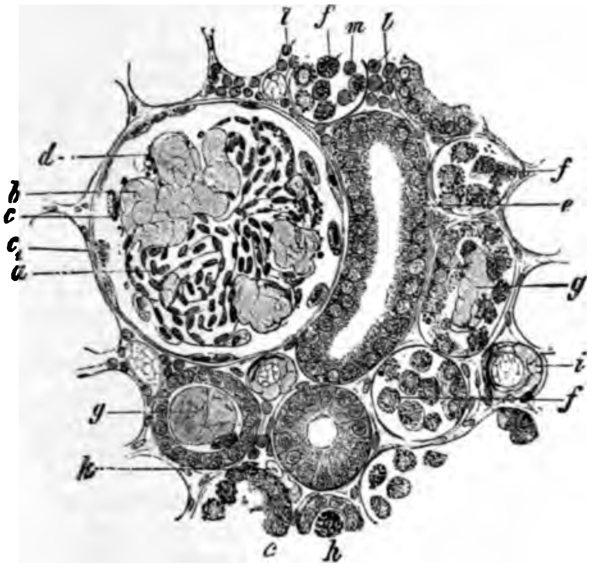


FIG. 62.—Section of an amyloid kidney. *a*, Normal vascular loops; *b*, Loops affected with amyloid disease; *c*, Fatty glomerulus epithelium; c_1, Fatty capsule epithelium; *d*, Fat-drops lying against the outer surface of the capillaries; *e*, Fatty epithelium *in situ*; *f*, Desquamated and fatty epithelium; *g*, Hyaline coagulations (urinary casts); *h*, Transverse section of a cast composed of fat-drops; *i*, Amyloid artery; *k*, Amyloid capillary; *l*, Cellular infiltration of the connective tissue; *m*, Round cells within the uriniferous tubules. (Magnified 300 diameters. Specimen treated with Müller's fluid, perosmic acid, and methyl violet.)

function observed in cases of amyloid disease, are *the pronounced change in structure* of the affected tissue, and *the degenerative changes in the cells of the affected organ*. Amyloid disease, consequently, has a distinctly degenerative quality. The connective tissue itself is permanently changed, as the insoluble amyloid substance would appear never to be removed from it, and it is self-evident that the function of organs thus affected must be seriously impaired.

The deposit of amyloid material in the blood-vessels leads to very considerable thickening of their walls, and at the same time to narrowing or even obliteration of their lumina, both of which conditions entail permanent interference with the circulation. The amyloid masses compress the surrounding epithelial structures and cause them to atrophy, and at the same time, on account of the impaired circulation, they may undergo fatty degeneration. These changes are well seen in amyloid degeneration of the liver, in which the liver-cells are always more or less deformed and atrophied as the result of pressure, and are often in a condition of pronounced fatty degeneration. In the kidney, also, fatty degeneration of the tubular epithelium is a prominent characteristic of the amyloid change, though it should be remembered that other conditions occurring in association with the amyloid disease may contribute to this change, and that on that account the degree of fatty change is not to be relied upon as indicative of the intensity of the amyloid disease, being often very extensive where the amyloid change is but slight.

In the spleen and lymph-glands, also, the cells lying in the meshes of the swollen trabeculæ disappear as the result of atrophy and fatty degeneration (Fig. 63, *f*), and in muscles the contractile substance diminishes *pari passu* with the increase of the amyloid material.

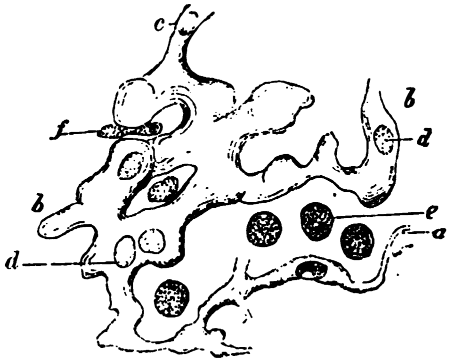


Fig. 63.—Amyloid swelling of the reticulum of a lymphatic gland. (After Eberth.) *a*, Normal reticulum; *b*, Swollen reticulum; *c*, Nucleus still unaffected; *d*, *d*, Degenerated nuclei; *e*, Normal lymph-corpuscles; *f*, Atrophic lymph-corpuscles. (Magnified 350 diameters. Methyl-violet preparation.)

Regarding the **causes** and **nature of amyloid degeneration** but little can be stated with certainty. We know that it is of most frequent occurrence in the *various cachectic states*, but we are wholly in the dark as to the precise perversions of nutrition which bring it about. The diseases with which it is most frequently associated are tuberculosis of the lungs and of the bones, syphilis, chronic dysentery, and leucæmia, and often in these diseases the most extensive amyloid degeneration will be found, while in the cachexia resulting from carcinoma it is but rarely observed. Occasionally it occurs without any discoverable preëxistent disease, and observations by Cohnheim would make it appear that it may become well developed in from two to three months.

Amyloid change which is widely distributed throughout the body must result from general causes. *The amyloid substance itself does not exist in the blood, but the material from which it is formed is undoubtedly derived from the blood*, and it would appear that the lowered vitality of the tissues resulting from general cachexia favors its formation. Perhaps in the conditions mentioned this peculiar amyloid substance results from the union of an albuminous material derived from the blood with some constituent of the tissues; or, as the result of impaired nutrition, a peculiarly modified albuminous body may be separated from the albumin in the circulation

Virchow and Kyber have drawn a parallel, and very properly as it seems to me, between amyloid degeneration of tissues and calcification. In both, a tissue of lowered vitality, because of impaired nutrition, becomes filled with a substance brought to it by the blood, and becomes intimately combined with substances preëxisting in the tissue. Wagner considers amyloid material to be the result of a retrograde metamorphosis of the albuminates, or more definitely as an intermediate stage between them and fat. Von Recklinghausen advances the hypothesis that in amyloid formation a homogeneous material is formed by the cells and, constantly washed by the lymph, swells and conglomerates, similarly to mucus, forming itself into small masses, reticula, membranes, or tubes. It has seemed to me that the amyloid material must be derived from the circulating blood, and I would venture the opinion that, as the result of the lowered metabolic power of the tissues, the substance thus derived cannot be converted, as under normal conditions, into nutritive matter, but lies in the tissues and undergoes metamorphosis into the peculiar material which we term amyloid.

Czerny believes that the precursor of amyloid is to be found in the white blood-corpuscles.

§ 68. The form of amyloid degeneration which we have thus far considered is a disease which usually affects a number of organs of the body, or, if confined to one of them, is more or less uniformly distributed throughout its entire substance. There is, however, a form of amyloid change in which localized deposits of amyloid material occur either in the form of *localized amyloid infiltrations of the tissues* or as *free concretions*.

Local amyloid infiltrations are met with in granulations which are rich in cells, in chronically inflamed tissues, in cicatrices, and in hyperplastic connective-tissue growths. They occur also in tumors in which other degenerative processes are in progress. In some cases only small particles of amyloid material are formed, and then frequently in the walls of the vessels; but in other cases large masses are met with, composed almost entirely of amyloid substance and often almost as hard as wood.

The *amyloid substance is here also deposited in the basement substance of the tissue*, though it is held by some authors (Rählmann) that the cells of the tissue may also acquire a hyaline appearance and give the reactions characteristic of amyloid.

Such local amyloid deposits have been found in the inflamed conjunctiva, in syphilitic scars in the liver, tongue, and larynx, in inflamed lymph-glands, in ulcers of bone, and in tumors of the larynx and stomach. Tumor-like amyloid masses are also occasionally met with in the conjunctiva, tongue, larynx, and trachea under conditions in which it is impossible to establish any relationship between them and some inflammatory process, and where, besides, there is but little normal connective tissue in the vicinity of the amyloid masses.

Freely lying amyloid concretions, or **corpora amylacea**, are most often found in the tissues of the central nervous system, especially in the spinal cord and in the ependyma of the cerebral ventricles. They occur also in the prostate gland. Those found in the nervous system are for the most part small, homogeneous, and somewhat shining particles (Redlich), usually devoid of any definite nucleus (Fig. 64, *c*). In the prostate they are larger and usually show distinct stratification (Fig. 64, *a*). Wagner and Langhans have observed corpora amylacea in carcinomata, and they have also been found in the lung (Friedreich, Zahn, Ziegler), in inflammatory areas, in bloody extravasations, and in emphysema.

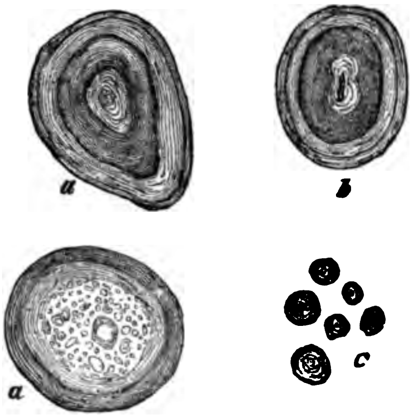


FIG. 64.—Corpora amylacea.
a, Laminated concretions from the prostate. (Magnified 200 diameters.)
b, Corpus amylaceum from an old hæmorrhagic infarction of the lungs, with hæmatoidin crystals in the nucleus. (Magnified 200 diameters.)
c, Corpora amylacea from the spinal cord. (Magnified 400 diameters.)

These local deposits of amyloid material and the amyloid concretions should not be considered as altogether similar to the progressive amyloid change to which we apply the term amyloid degeneration. Some of them, it is true, give the characteristic amyloid reaction, and the corpora amylacea of the nervous system, in particular, assume the characteristic blue color when treated with iodine and sulphuric acid. But, in the case of these bodies, we have to do with formations dependent essentially upon local conditions for their origin, and it can hardly be disputed that they are formed from the albumin of the affected tissue. The concretions of the prostate are made up of degenerating epithelium or of fragments of the same matted together in layers, and it is probable that the similar bodies in the lung and in tumors are composed chiefly of fragments of degenerated cells, though in part, also, of albumin from the blood. Redlich considers the corpora amylacea of the nervous system, which stain similarly to nuclei with hæmatoxylin, to be made up of the nuclei of neuroglia-cells and to be a senile retrograde development of the tissue. Stroebe, however, believes them to be composed of fragments of swollen axis-cylinders, while Siegert believes them to have originated from cells.

X. Hyaline Degeneration of Connective Tissue.

§ 69. **Hyaline degeneration** is naturally taken up next in order after amyloid degeneration, both because of the appearance of its product and because of its occurrence in connective tissue and in blood-vessels. But it does not give the reactions characteristic of amyloid.

When hyaline degeneration begins there is usually a degeneration of the walls of the smaller vessels (Fig. 65, *a*), as the result of which a hyaline material, strikingly similar to amyloid, but differing from it in reactions, is formed just externally to the endothelium of the vessels, making their walls thicker and narrowing their lumina, until the vessels may become very narrow tubes whose outline is made irregular by the presence of the hyaline material in their walls. Finally, the lumen of the vessel

Fig. 65.

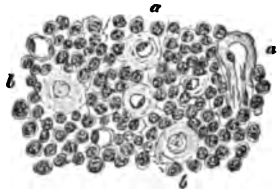


Fig. 66.

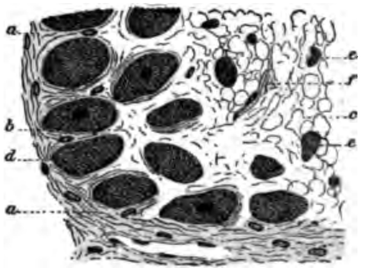


FIG. 65.— Hyaline degeneration of the blood-vessels of an atrophic lymph-gland from the axilla. *a*, Vessels which have undergone hyaline degeneration, but still possess an open lumen; *b*, Obliterated vessels. (Specimen hardened in alcohol and stained with alum carmine and picric acid; and the section mounted in Canada balsam. Magnified 200 diameters.)

FIG. 66.—Hyaline degeneration of the connective tissue of the myocardium. *a*, Normal connective tissue; *b*, Connective tissue that has undergone hyaline degeneration; *c*, Hyaline masses; *d*, Transverse sections of normal muscle-cells; *e*, Transverse sections of muscle-cells which are atrophic. (Preparation treated with hæmatoxylin and neutral carmine, and mounted in Canada balsam. Magnified 250 diameters.)

may be completely obliterated, in which case its endothelium, which may have remained practically unaltered or may have even proliferated up to that time, disappears. Occasionally the hyaline substance is deposited in drop-like masses in the immediate neighborhood of the vessels, but without compressing their lumina. These changes are most frequently met with in the vessels of the glomeruli of the kidney and in those of the thyroid, brain, lymph-glands (Fig. 65), choroid, and retina (in cases of lead-poisoning) (Oeller). Vossius and others have shown that the conjunctiva may be the seat of tumor-like growths, composed of adenoid tissue, in which the reticular basement substance becomes hyaline, swells, and acquires a knotty appearance, and in which the cells undergo atrophy.

The mode of formation of these hyaline masses cannot be stated with positiveness, though it would appear likely that the walls of the vessels and the connective tissue become infiltrated with a liquid of some sort which coagulates. It is possible, also, that the leucocytes and blood-plates furnish a portion of the hyaline substance, and Oeller believes that red blood-corpuscles also participate in its formation.

Occasionally, though rarely, hyaline degeneration typical in appearance is met with in fibrous connective tissue—as, for example, in the connective tissue of the heart, intestine, and thyroid gland—and may then cause a material increase in volume of the connective tissue of the organ (Fig. 66, *b*). In the early stages of this process the connective tissue appears uniformly homogeneous and loses its fibrillar appearance; later, distinct masses of hyaline material form, just as was described in connection with amyloid degeneration. In this process everything included in the degenerated area degenerates and disappears—both parenchyma and connective-tissue cells.

These changes are unquestionably closely related to those which occur in amyloid degeneration, both in appearance and in significance, for portions of the hyaline material may undergo conversion into amyloid, thus causing combinations of the two forms of degeneration.

A second variety of hyaline degeneration of connective tissue, to which Virchow has applied the term **sclerosis**, occurs in old age as a rather frequent affection of the intima of the valves of the heart and of the arteries. It is also met with in strumous thyroid glands, in cicatrices, and in the connective-tissue stroma of tumors.

As in the first-mentioned form of hyaline change, the tissue acquires a homogeneous appearance and becomes thickened and actually increased in volume to a certain extent. The contained cells, which are at first preserved, ultimately undergo fatty degeneration in most cases and disappear. Finally calcification of the hyaline material may occur.

The origin of this variety of degeneration is shrouded in even greater obscurity than that of amyloid degeneration. There can be no question as to its being a form of retrograde change, and since there is moderate increase in volume of the affected tissue, it is probable that a deposit of some sort occurs in it. Whether the mode of development of this variety of hyaline degeneration is the same as that of the first-described variety, differing from it only quantitatively, is questionable. The degenerated areas react similarly in both cases to staining solutions and reagents, although to the naked eye the sclerotic areas appear to be less translucent than the others.

The preparation pictured above (Fig. 66) was obtained from the heart of a woman about fifty-five years of age, the greater part of which had undergone hyaline degeneration. Numerous hyaline plates and masses were found in the endocardium and pericardium. The muscle-tissue was in parts degenerated as shown in the figure. Associated with this condition in the heart there was extensive degeneration of the blood-vessels, particularly of the intestine, tongue, lungs, heart, and bladder. The peritoneum was also thickly bestrewn with hyaline masses. The fact that the smaller hyaline areas and the periphery of the larger areas gave no iodine reaction, while the central portions of the larger areas did so, appears to me to make the close relationship between hyaline and amyloid substance unquestionable. And this is further supported by the fact that amyloid organs occasionally contain areas of hyaline degeneration. It would therefore appear permissible to advance the hypothesis that amyloid substance is formed from a hyaline albuminous body not reacting to iodine, but that the transition from the one to the other usually occurs very quickly.

Litten[*] has made the observation that portions of amyloid tissue introduced into the abdominal cavity of animals undergo a change, in the course of several months, as the result of which they lose their power to react to iodine and methyl violet, although their transparence and homogeneity are preserved. From this it would seem that amyloid may at times be converted into hyaline material.

Van Gieson's method of staining connective tissue is well adapted to the detection of hyaline. It consists of overstaining with hæmatoxylin, and of decolorization and contrast-staining with watery solution of picric acid which has been made of a light-red color by the addition of a few drops of acid-fuchsin solution. With this stain the hyaline material takes on a brilliant red color, while amyloid assumes a more orange color.

XI. Calcification and the Formation of Concretions and Calculi.

§ 70. It is, on the whole, a rather frequent occurrence for crystals, or amorphous and granular masses, to be precipitated here and there in the body; and when such deposits are in sufficient amount to cause hardening of the affected tissue, the resultant condition is spoken of as **petrifaction**, or, when the deposited material consists of lime-salts, as **calcification.**

Such deposit may occur in tissue which forms an integral part of an organ and which bears its normal relation to the surrounding tissues. In other cases it may form an incrustation around tissues which have been separated in some manner from their surroundings, or around foreign bodies which have found their way into the body from without, and have then become the centres of a process of incrustation.

In the first case **calcification of the tissue** results; in the second, **free concretions and calculi** are formed. It is to be remembered, however, that concretions which may have been at first free may occasionally become firmly attached to the tissues of the organ in which they lie by growth into them of some of the surrounding tissue; and, on the other hand, a portion of calcified tissue may gradually undergo separation from the surrounding tissue and ultimately form a free concretion.

The *cause of calcification is for the most part to be found in local changes in the tissues*, since the deposit of lime-salts usually occurs in localities in which the tissue has already died or is in process of degeneration and necrobiosis. It looks as if dying tissue, which has undergone more or less modification, possesses a kind of attraction for the lime-salts in solution in the body, and enters into intimate combination with them. Among the degenerating or dead tissues which are particularly prone to undergo calcification we may mention in particular connective tissue (§ 69) which has undergone hyaline degeneration; such connective tissue being quite often encountered in the walls of the blood-vessels, in the endocardium, in an enlarged and degenerated thyroid, or in thickenings of the pleura or pericardium. It is common, also, in degenerative areas in the walls of blood-vessels, or in tumors, or in any other portion of the body in which hyaline and fatty degeneration are in progress; in degenerating cartilage; in dead cell-bodies, as, for example, in dead ganglion-cells (Fig. 68) or kidney epithelium (especially in corrosive-sublimate, aloin-, or bismuth-poisoning); or in circumscribed cheesy areas of considerable size.

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[*] "Ueber die Amyloiddegeneration," *Deutsche med. Wochenschrift*, 1877.

Calcification occurs, also, at times in tissues which have undergone much less degeneration and in which there are still living cells; and under very exceptional conditions it may take place in tissues which show no recognizable change. This occurs more particularly in advanced age, when the lime-salts of the skeleton are undergoing more rapid absorption, in which case they may be deposited in the lungs as well as in the kidneys and in the mucous membrane of the stomach.

The lime-salts are deposited in the form of small granules (Figs. 67 and 68), and preparations are occasionally met with in which the separate calcareous granules are still visible.

Fig. 67.

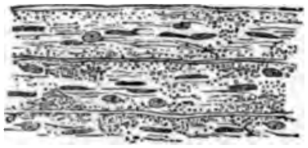

Fig. 68.

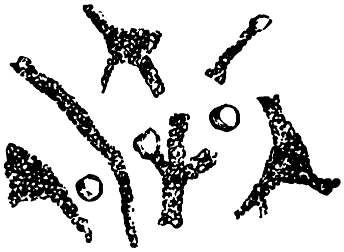

FIG. 67.—Calcification of the media of the aorta. (Magnified 350 diameters.)

FIG. 68.—Calcified ganglion-cells from the brain of a demented person affected with hemiplegia and with a dropsical effusion in the ventricle of one side. (Magnified 500 diameters.)

As the result of conglomeration of these granules, larger masses and spherules may be developed (Fig. 68). More frequently, however, a more homogeneous deposit forms, in which it is impossible to distinguish the individual granules.

Both cells and intercellular substance may undergo calcification, and when calcification is in progress the degenerated tissue comports itself somewhat differently toward certain stains than normal, unchanged cell-protoplasm or intercellular substance does. Thus hæmatoxylin imparts a dirty bluish-violet color to it, and it usually stains red with picrocarmine. This applies, however, only to deposits of carbonates and phosphates of lime, not to those of oxalate of lime.

Calcification may affect small or large areas of tissue, causing, in the latter instance, distinct hardening of the tissue and a whitish coloration. At times such calcified areas are sharply separated from the surrounding tissue in the shape of spheroidal, spindle-shaped, or cactus-like masses (Fig. 69 and Fig. 70, *a*, *b*, *c*, *d*), being in reality **concretions lying in the**

tissue. Not infrequently these are of sufficient size to be readily visible to the naked eye. Such concretions occur physiologically in the form of stratified calcific spherules in the pineal gland and in the choroid plexus, and are then known as *brain-sand* (*acervulus cerebri*). Pathologically they are met with in various localities in the pia and dura mater, in tumors of these membranes (psammomata—Fig. 70), in cheesy areas (Fig. 69, *b*), and in nodular growths of connective tissue (Fig. 69, *a*).

Fig. 69.

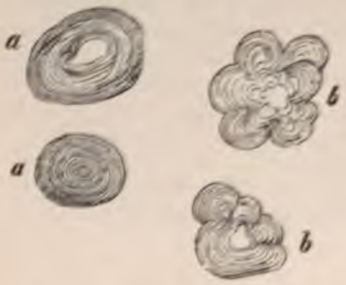

Fig. 70.

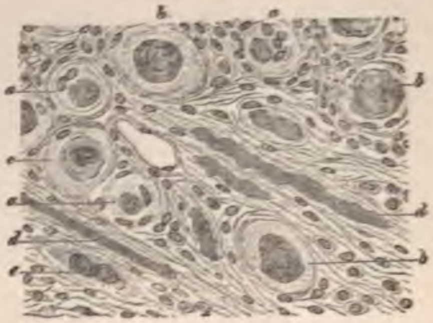

FIG. 69.—Calcareous concretions. *a*, Concretions from an inflamed omentum; *b*, Calcareous glands from a tubercular lymph-gland that has undergone cheesy degeneration. (Magnified 200 diameters.)

FIG. 70.—Section of a psammoma of the dura mater, with calcareous formations. *a*, Hyaline nucleated balls with an inclosed grain of calcareous material; *b*, Calcareous formations surrounded by a non-nucleated hyaline substance encapsulated in an envelope of fibrous connective tissue; *c*, Calcareous nodule surrounded by hyaline connective tissue; *d*, Calcareous spiculæ in the connective tissue; *e*, A calcareous spicule, with three separate concretions, embedded in the connective tissue. (Specimen hardened in alcohol and then decalcified in picric acid; the section stained with hæmatoxylin and eosin. Magnified 200 diameters.)

The formation of these bodies may perhaps be best described as it occurs in the psammomata. Some of the cells of the tissue (Fig. 70, *a*, *b*, *c*) or a circumscribed area of connective tissue (Fig. 70, *d*) undergo hyaline degeneration, the nuclei being at first preserved, but later lost. In this way small hyaline spherical areas are formed, and in these the deposit of lime-salts takes place. The more spheroidal concretions would appear to be formed from masses of degenerated cells, while the longer, spindle-shaped concretions seem to have their origin in the connective tissue, though it would seem that the spheroidal masses may also be formed in it. The variety of connective tissue which undergoes this calcification is the ordinary white fibrous tissue, but concretions may also occasionally form in the connective tissue surrounding the blood-vessels.

§ 71. The ordinary petrifaction or calcification of the tissues results from a deposit of carbonate and phosphate of lime, to which occasionally magnesium-salts are added. In certain states of the body, however, a **deposit of uric-acid salts** takes place. This is notably the case in **gout,** in which an excess of uric acid accumulates in the body as the result of chronic disturbance of nutrition.

Gout is usually inherited, though it may occasionally be acquired. It is of very frequent occurrence in England and in northern Germany, but is rare in other localities, as, for example, in southern Germany. As to its ultimate cause we know practically nothing. It is characterized chiefly by the deposit in the body of urates (Fig. 71, *b*), particularly of sodium urate, with which small quantities of carbonates and phosphates are sometimes associated. The deposit of these salts is usually accompanied by symptoms of a very acute nature—pain and inflammation; though at times, when the deposit takes place very slowly, there may be no characteristic acute attack. The kidneys and the skin and subcutaneous tissue are perhaps most often affected, though deposits may also take place in the tendon-sheaths, the tendons, ligaments, synovial membranes, and articular cartilages (Fig. 71), and may ultimately be found in nearly every organ of the body. The metatarsophalangeal joint of the great toe is a favorite site. The deposits consist for the most part of bunches of fine acicular crystals (Fig. 72) and lie usually in necrotic tissue, which fact has led Ebstein to infer that the urates cause necrosis of the tissue in which they have been deposited.

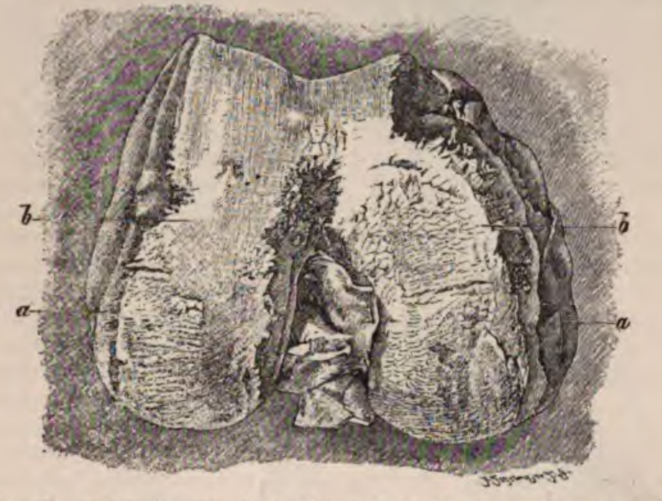

FIG. 71.—Deposits of urates in the knee-joint, in a case of gout. *a*, Condyles of the femur; *b*, Deposits of urates upon the cartilaginous surface. (Two-thirds natural size.)

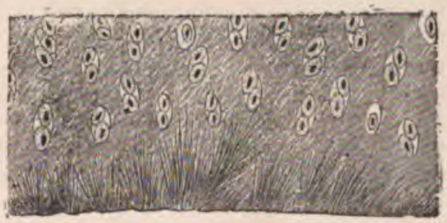

FIG. 72.—Deposit of needle-shaped crystals of urate of soda in the articular cartilage. (After Lancereaux. Magnified 200 diameters.)

The areas in which this incrustation and necrosis have occurred are at first small, but soon cause inflammation and proliferation in the surrounding tissue. These areas, with the occurrence of fresh deposits, may increase in size, and in this way often attain, after a time, considerable dimensions. These larger deposits are called *tophi*. They consist of white, plaster-like substance, and at times form large rounded masses, more especially in the joints and tendons (Fig. 73).

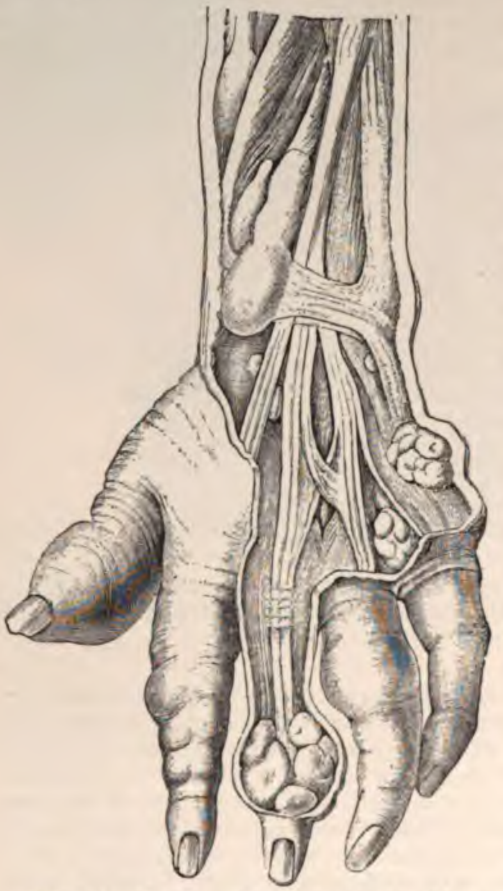

FIG. 73.—Gouty nodes of the hand. (After Lancereaux.)

In the joints the articular cartilage looks at first as if it had been sprinkled over with plaster of Paris (Fig. 71, *b*), but with time the white substance penetrates deeper and deeper into it, until finally it may permeate the whole cartilage. In the kidney the necrosis of tissue and inflammatory condition consequent upon a deposit of urates may lead to induration and contraction of the organ. The deposit is more abundant in the medullary substance of the kidney, but is also met with in the cortex.

According to Garrod and Ebstein, the acute exacerbation in gout depends upon excessive accumulation of uric acid, either as the result of deficient excretion by the kidneys (Garrod) or because of local changes in the affected tissue (Ebstein). Pfeiffer explains it by supposing that the deposits of salts depend simply upon the presence in excess, in the body-liquids, of a substance which is soluble with difficulty in them, and which therefore may very readily be deposited in various parts of the body, sometimes accumulating there in such quantity as to induce a localized necrosis. The symptoms of the attack are supposed to depend upon a temporary increase in alkalinity of the liquids of the body, enabling them to dissolve and absorb a portion of the deposited salts, in the course of which procedure pain and inflammation are induced. Von Noorden, on the other hand, considers uric-acid formation and deposit to be a secondary phenomenon, caused by the presence of a localized ferment of some sort, and quite independent of the amount and condition of the uric acid formed in other parts of the body.

§ 72. **Free concretions** occur most often in ducts and in cavities of the body which are lined by epithelium, as in the intestine, in the ducts of the glands pouring their secretions into the intestine, in the gall-bladder, in the urinary passages, and in the respiratory passages. The concretions occasionally met with in the lumina of vessels and in serous cavities might also be included in this group, although they are for the most part closely bound to the surrounding tissue.

All free concretions have an organic basis or nucleus. Thus *enteroliths* which form in the intestine have a basis of inspissated fæces, or hairs (bezoar-stones, ægagropilæ), or indigestible vegetable material, or something of the sort, in which phosphates of ammonia, magnesia, and lime, and carbonates are deposited in varying proportions, according to the nature of the food taken. The *tartar* of the teeth is formed by the deposit of lime-salts in particles of food, mucus, or masses of bacteria, which collect upon the teeth; and it is probable that the calculi which form in the ducts of the salivary glands and in the ducts of the pancreas originate primarily from a substance derived from the epithelium.

Bronchial calculi result from the deposit of lime-salts in dried and thickened bronchial secretion; and the stones found in arteries and veins, from calcification of thrombi.

Gall-stones often seem to be made up entirely of crystalline material; but by the employment of suitable methods of examination it is always possible to show that they also contain a nitrogenous basis. They are for the most part spheroidal or faceted concretions of various sizes, whose cleavage suggests a crystalline structure. Several varieties of gall-stones are, in fact, distinguished according to the substance deposited in them.

Thus there are gall-stones composed of cholesterin alone, or cholesterin and bile-pigment, others of bilirubin, others of biliverdin and lime, and still others of carbonate of lime alone. The most frequent are the first two, and the calculi composed of them have a ray-like, crystalline, and sometimes stratified cleavage, and are white or colored in proportion to their content of bile-pigment.

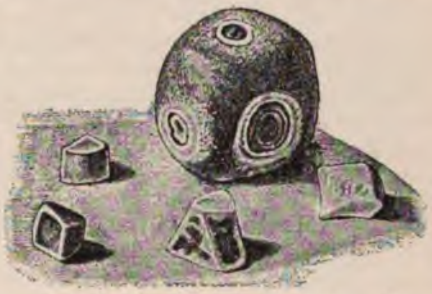
FIG. 74.—Faceted concretions from the gall-bladder. (Natural size.)

If the cholesterin of one of these gall-stones be dissolved out by ether, it will be found that a rather yellowish substance remains, which preserves the shape of the original stone, and which, when embedded and cut for microscopic examination, will be found to consist of a delicate homogeneous material (Fig. 75) in which there are usually radiating spaces formerly occupied by the crystals, and which frequently shows concentric stratification. It is possible to demonstrate a similar ground-substance in other calculi after solution of their contained salts.

There can, then, be no doubt that gall-stones also are the result of incrustation of an organic substratum in all probability derived from the mucous membrane of the bile-ducts and gall-bladder. Gall-stones are more apt to form in advanced life. Naunyn is very positively of the opinion that stagnation of the bile in the biliary passages is a universal cause of their formation, that this condition and disease of the mucous membrane lead to desquamation and degeneration of the epithelium, and that in this débris the deposit of cholesterin and bile coloring-matters takes place. In conformity with this view is the fact demonstrated by Steinmann that albuminous substances are capable of precipitating lime from solutions in which it is present as chloride or sulphate, in the form of carbonate; and he has shown that the shells of mollusks are produced by calcification, in this way, of mucous material elaborated by the mantle epithelium. When a concretion has once started, its growth continues as the result of fresh deposits of degenerated material which is incrusted with cholesterin and bile-pigment as before, and so on. At the same time the original softer nucleus of the concretion undergoes a change in that its solid ingredients seem to be attracted to the denser periphery of the stone, while its organic ingredients may liquefy. This accounts for the occasional presence of a cavity filled with liquid in the centre of gall-stones. In time cholesterin fills this cavity and in great part replaces the bile-pigment in the remainder of the stone. Carbonate of lime may also be deposited.

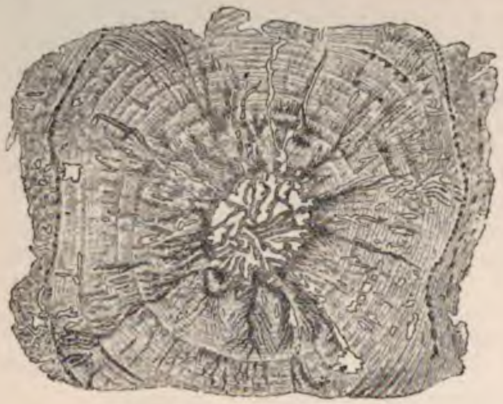

FIG. 75.—Transverse section of a small so-called cholesterin calculus after the removal of all the cholesterin. (Magnified 15 diameters.)

Gall-stones consequently occur where epithelium of the mucous membrane is degenerating, and it is probable that much of the cholesterin which composes these masses is derived from its protoplasm. The chalky deposits stained with bilirubin have their origin in the lime-salts secreted by the mucous membrane, and their precipitation would appear to be aided by the presence, in the secreted mucus, of the degenerating albuminous material. Of course the cause of the epithelial degeneration is inflammation of the bile-passages, which may be brought about by stagnation of the bile, or perhaps, also, by penetration of bacteria into the common duct.

Finally, Ebstein has shown that the *concretions and calculi found in the urinary passages* are also composed of an albuminous stroma in which various ingredients of the urine have been deposited. These concretions are described, according to their situation, as occurring in the kidney or in the urinary passages leading from it. In the kidney they are, as a rule, small deposits which, as already alluded to in §§ 70 and 71, may form in the tissue of the kidney or in the lumina of the urinary tubules, in which latter case they are interspersed with débris of the tubular epithelium. This is true, for the most part, of the calcifications which are observed in cases of poisoning by corrosive sublimate, bismuth, and aloin, and, more rarely, in poisoning by phosphorus, potassium chromate, and oxalic acid. It is also true of at least some of the gouty deposits. Furthermore, concretions of uric acid are frequently met with in the uriniferous tubules of children who have died during the first two weeks or so of life. They impart to the medullary portion of the kidney a distinct streaked, yellowish appearance, the condition being spoken of as *uric-acid infarction of the new-born*. The epithelium lining the tubules in which these concretions are found is for the most part well preserved, but in places slight desquamation and degeneration of the desquamated cells will be found. In the lumina of the tubules are many small spherules (Fig. 76, *b*), radially striated, colorless, or slightly brownish, and composed chiefly of urates or of uric acid. On solution of the uric acid a fine delicate stroma remains (Fig. 76, *c*). If, as the result of the presence of these concretions, further desquamation and degeneration of the epithelium takes place, leading to the formation of considerable albuminous degenerated material in the tubules, some of the smaller concretions may gradually grow, as the result of accretion, to stones of considerable size; but this is unusual.

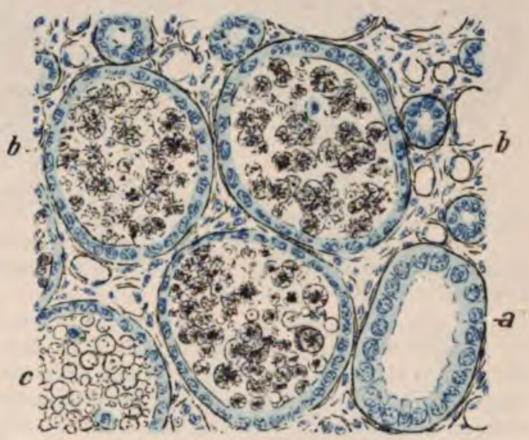

FIG. 76.—Uric-acid infarction from a new-born child. Transverse section of a pyramid of the kidney. *a*, Collecting-tube of the papillary zone of the medullary portion, seen in transverse section and as yet in a normal condition; *b*, Dilated collecting-tubes filled with uric-acid concretions; *c* shows what remains in one of these tubes after the concretions have been extracted by the aid of water. (Specimen hardened in alcohol, stained with hæmatoxylin, and mounted in Canada balsam. The part at *c* was drawn from another specimen which had been allowed to soak for some time in water. Magnified 200 diameters.)

Concretions may also form in the pelvis of the kidney, in the ureters, in the bladder, in the urethra, or even under the prepuce, in the form of sand, gravel, or calculi. The last-mentioned are spheroidal or oval in shape, as a rule, and may be smooth upon the surface, or rough, mulberry-like or coral-like (Figs. 77 and 78). When several stones lie together, their adjacent surfaces usually become faceted, as shown in Fig. 78. When they occupy the pelvis of the kidney, their shape not infrequently quite accurately represents the shape of the pelvis.

Seen in section, urinary calculi are sometimes homogeneous, at other times distinctly stratified (Fig. 78) or radially streaked, and often show a nucleus and several distinct zones of different appearance. Ebstein has shown that in these calculi, also, an organic substance, albuminous in nature, is left after solution of the various salts. In stratified calculi this stroma also shows stratification, often with radially disposed slits.

When stratification is absent, it is composed of a network of irregular construction, or, more rarely, of a homogeneous mass. There would seem to be little doubt that the crystalline bodies are deposited in this stroma, partly in the spaces and partly in its substance; and it is also most probable that the stroma itself is a product of the mucous membrane of the urinary passages, whose formation is assisted by the accumulation of débris and mucus consequent upon catarrhal inflammation or toxic degeneration of the epithelium.

Fig. 77.

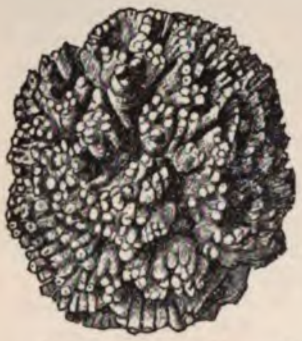

Fig. 78.

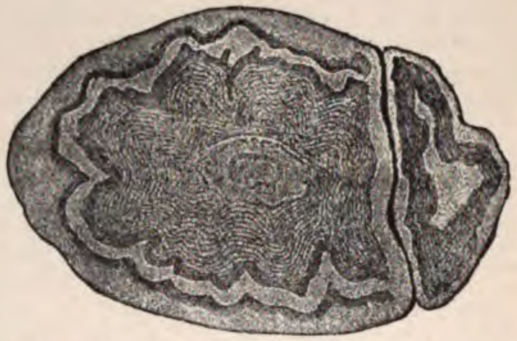

Fig. 77.—Coral-shaped stone from the bladder, composed of oxalate and phosphate of lime. (Natural size.)

Fig. 78.—Transverse section of two stones from the bladder, closely fitted together, and composed of urate of soda and ammonio-magnesium phosphate. (Natural size.)

What particular substances are deposited in any given case of stone-formation depends upon a variety of circumstances. When the uric-acid diathesis is present coincidently with the condition of epithelial degeneration necessary to the formation of a calculus, urates are usually deposited. Decomposition of the urine, with formation of ammonio-magnesium phosphate, gives the condition necessary for the formation of a phosphatic calculus. Cystin calculi may form when cystin is excreted by the kidneys as the result of peculiar metamorphoses of albuminous material in the intestine, brought about by bacteria (Baumann, von Udransky, Brieger). When a calculus has once begun to form, the irritation of the mucous membrane which it produces, and the decomposition which results from stagnation of the urine, cause its further growth by fresh accretion, and in the same way *foreign bodies* which have in any manner found their way into the bladder *may act as a nucleus for a calculus.*

Urinary calculi are classified according to the substances of which they are composed, as follows:

1. *Calculi composed chiefly of uric acid or urates.*

Pure uric-acid calculi are for the most part small, hard. They are yellowish, reddish, or brownish in color.

Calculi of urates are rarely pure. They are usually covered on the surface by coatings of oxalate of lime and ammonio-magnesium phosphate.

2. *Calculi composed chiefly of phosphates and carbonates.*

To this group belong *calculi composed of calcium phosphate, ammonio-magnesium phosphate, and calcium carbonate.* The last mentioned are rare. All these calculi are white or grayish. Those composed of the triple phosphate are soft and friable; the others are hard.

3. *Calculi composed of calcium oxalate.* They are hard and rough. Their color is brown.

4. *Calculi composed of cystin.* These are soft, waxy, and brownish yellow.

5. *Calculi composed of xanthin.* These are cinnabar red in color, smooth, and their fracture is earthy.

Ebstein and Nicolaier succeeded in producing urinary calculi artificially by feeding animals with oxamide, an ammonium derivate of oxalic acid, as the result of which concretions of a greenish-yellow color formed in the urinary passages of dogs and rabbits. These were found to be composed of oxamide and to have a concentrically stratified structure with radial striations. They possessed an albuminous stroma, which resulted from desquamation and necrosis of the tubular epithelium induced in the excretion of the oxamide.

XII. Pigment-formation in the Tissues.

§ 73. **Pigment** is normally present in connective and epithelial tissues in several parts of the body (**autochthonous pigment**). It lies within the cell-bodies and consists of yellow, brown, and black granules, or is diffuse, imparting its color to the cell-protoplasm. Among the epithelial structures containing pigment may be mentioned the deepest layers of the rete Malpighii which in all the colored parts of the skin contain pigment, the hairs, the pigment epithelium of the retina, and many ganglion-cells. In the skin the pigment granules are for the most part yellow and brown; in the retina, black (*melanin granules*). When the skin is unusually dark, other layers of the rete Malpighii contain pigment also. Among the connective-tissue structures which may contain yellow or brown pigment granules are the cells of the pia, of the choroid, of the sclerotic, of the cutis vera, and of the heart-muscle.

Under various physiological and pathological conditions this normal **pigment**, of autochthonous origin, may increase in amount. Thus *during pregnancy the pigment of the skin usually increases more or less* (*chloasma uterinum*), particularly in brunettes. In *Addison's disease*, which would appear to depend upon changes in the suprarenal capsules, decided pigmentation of the skin occurs as the result of increase of the normal pigment. In atrophic conditions of the heart-muscle there is usually increase of its pigment, and atrophy of the voluntary muscles is often accompanied by an accumulation of yellow

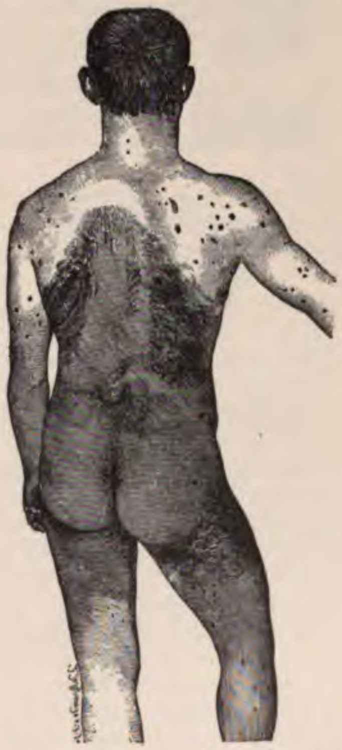

FIG. 79.—Large hairy pigmented mole over the lower part of the back and on the posterior aspect of the hip, with scattered spots of discoloration over the trunk and shoulders. (From Röhring.)

pigment in the fibres. In old persons the smooth muscle-fibres of the intestine always contain more or less pigment.

The most intense grades of pathological pigmentation are met with in *freckles*, in *pigmented moles* (Fig. 79), and in various pigmented tumors (*melanotic tumors*). The amount of pigment may be so great as to impart a perfectly black color to the tissue.

The pigment is for the most part contained in the cell-bodies, though it is occasionally in the intercellular substance also, and is composed of yellow, brown, or black granules. Occasionally cells are diffusely colored. In Addison's disease the pigment granules are situated partly in the epithelial cells lying next the connective tissue of the cuticle (Fig. 80) and partly in branched connective-tissue cells, some of the pigmented branches, as a rule, extending up between the epithelial cells.

In pigmented spots in the skin and in melanotic sarcomata the pigment is to a great extent contained in large, specially differentiated connective-tissue cells, in part also in ordinary connective-tissue cells in the neighborhood of blood-vessels and in their walls.

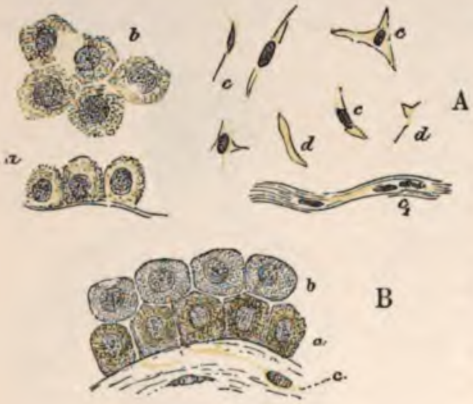

FIG. 80, A and B.—Pigmented cells of the skin, from a case of Addison's disease with cheesy tuberculosis of both suprarenal capsules. *a*, Pigmented epithelial cells from the deepest layer in a section made at right angles to the surface; A, *b*, Pigmented epithelial cells from a section made in a plane parallel with the surface; B, *b*, Epithelial cells containing no pigment; c_1, *c*, Nucleated pigmented connective-tissue cells, the terminal processes of which push their way, in B, between the epithelial cells; *d*, Pigmented terminal processes of cells. (Specimen hardened in alcohol, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 350 diameters.)

So far as may be inferred from histological examination, *the pigments which we have been describing are the result of a special kind of cell-activity*, and we must suppose that many connective-tissue cells, ganglion-cells, and muscle-cells are able to form pigment out of the material brought to them. The pigment would appear to be formed for the most part where it is found, though it has been shown that it may at times be transported, and that the pigment of the skin in particular, as well as that of the hair, is, in part at least, formed in connective-tissue cells lying close under the rete Malpighii, and sending branching processes between its epithelial cells, from which the pigment is taken into the epithelial cells.

It is even more difficult to determine the source of the material from which the pigment is elaborated. The frequent proximity of the pigment to blood-vessels seems to indicate that its antecedents are derived from the blood, and many accept the theory without question that the pigment is derived from the coloring-matter of the blood. It is distinctly against this view, however, that when pigment is found in the neighborhood of vessels, these are not capillaries, as a rule, but arteries, from which escape of blood-pigment could hardly occur, and that any change in the blood itself, or in the neighborhood of the vessels, suggestive of breaking down of the blood-corpuscles and escape of pigment from them, is usually entirely lacking.

The attempt has consequently been made to solve this question by chemical means, with the result that several facts have been discovered tending to show that the pigments are products of cell-activity and are formed from albuminous bodies. In the first place, it has been shown that the various pigments differ to a considerable extent in composition. In the course of investigations in von Nencki's laboratory a brownish-black amorphous pigment containing a distinct but variable quantity of sulphur was separated from human hair. The pigment of the choroid was, on the other hand, shown to be devoid of sulphur. The metastases of a melanosarcoma, which had its origin in a pigmented mole of the skin, contained a pigment free from iron, but rich in sulphur, insoluble in alcohol, water, and ether, soluble in ammonia and alkaline carbonates. Von Nencki has named this pigment *phymatorhusin*. Two other melanosarcomata examined by von Nencki and Sieber, however, contained no phymatorhusin, and they are convinced that the pigment formed in Addison's disease is also different. Black pigment from a melanotic sarcoma of a horse was also iron-free and contained sulphur, though in smaller amount than the pigment from the human melanosarcoma. Von Nencki has called this *hippomelanin*. Carbone also failed to find iron in a melanosarcoma, while Brandl and Pfeiffer, on the other hand, found in a melanosarcoma 3.7 per cent. of sulphur and 0.52 per cent. of iron, and Mörner obtained 0.2 per cent. of iron from another. Finally, Wallach obtained a reaction for iron by treating portions of a melanosarcoma with aqua regia and potassium ferrocyanide.

Nothing can be said with certainty as to the source of the material from which the cells form pigment. The mere fact that the pigment of melanotic tumors contains iron is no proof that it is derived from the hæmoglobin, since tumors often contain disintegrated blood in addition to pigment. At all events, one finds here and there in melanosarcomata yellow granules which give the reaction of hæmosiderin (cf. § 74), while the majority of the pigment granules do not. But, on the other hand, failure to obtain a reaction for iron does not prove that a given pigment is not derived from the blood, as after a time changes occur in iron-containing pigments which make it impossible to obtain a reaction for iron. The high sulphur content of many of the pigments makes probable their origin from albuminous substances, and their frequent proximity to the blood-vessels would suggest that this albuminous material is derived from the blood, perhaps from the globulin of red corpuscles. The pigment of the so-called chloromata is of a fatty nature (*Lipochrom*), according to Krukenberg. These tumors have a light-green or dirty brownish-green color when freshly cut. It is quite likely that the coloring-matter of the egg-yolk and of the corpus luteum is also of this nature.

During the past few years the origin of the pigment of the skin has been the subject of much study and discussion among both anatomists and pathologists. Aeby was the first to express the belief that the epithelial cells themselves do not form pigment, but derive that which is found in them from wandering cells laden with pigment, which penetrate between the individual epithelial cells and then degenerate, the pigment and débris of the cells being taken up by the epithelium. According to von Kölliker, "the pigment of the hair and of the skin is derived from pigmented connective-tissue cells which send processes between the epithelial cells of the deepest layers of the hair-bulbs and of the rete Malpighii, which processes divide and subdivide, penetrating deeper and deeper between the cells, and in some instances even passing into the bodies of the cells themselves and depositing their pigment there. These pigmented connective-tissue cells are always confined to the deepest layers of the rete." The pigment of the ganglion-cells and of the cells of the retina is formed in these cells themselves. Riehl and Ehrmann concur with von Kölliker in this opinion. Karg has arrived at much the same conclusion, as the result of the study of the effect of grafting white skin on the floor of an ulcer of the leg in a negro. In the course of from twelve to fourteen weeks the grafted skin became quite black, like the skin of the rest of the negro's body. Examination showed fine pigmented processes, believed to be offshoots of connective-tissue cells, lying between the epithelial cells at a time when the epithelial cells themselves had not as yet become pigmented. Von Wild has also shown that in melanosarcomata of the skin the pigmented connective-tissue cells penetrate between the epithelial cells. The pigmented skin of persons affected with Addison's disease shows similar pigmented connective-tissue cells, though these are not always to be found everywhere in such cases.

Histological studies of the mode of formation of pigments in animals, which have been carried on chiefly on fishes, amphibia, and reptiles, have led to various conclusions. Thus Jarisch is of the opinion that the pigment of the skin and teeth of tadpoles is not derived from the blood, but is a product of the protoplasm of the cells, while List thinks that he can trace the pigment of the skin of fishes and amphibia to disintegrated red corpuscles. According to Kromayer, the pigment of the skin of mammals is derived from protoplasmic processes of the epithelial cells and represents a product of their degeneration.

A curious *pigmentation of the internal organs* is met with in some domesticated animals, occasionally associated with melanosis of the subcutaneous tissue, in which the heart, lungs, intestine, etc., contain grayish or black spots, looking like ink-spots, in varying numbers, and which are produced by the presence of pigment in connective-tissue cells otherwise apparently healthy.

Virchow has described, under the term *ochronosis of cartilage*, a peculiar pigmentation of cartilaginous structures, tendon-sheaths and synovial membranes by an iron-free pigment, whose imbibition into the matrix of the cartilage imparts to it a brownish or black color. He explains this on the supposition that blood-pigment has soaked into the stroma of the cartilage, and compares this form of pigmentation with that which occurs in freckles. It is probable that this condition is only a more pronounced form of the diffuse pigmentation especially noticeable in the costal cartilages of old persons. Occasionally this pigment is also deposited in granular form.

§ 74. **Hæmatogenous pigment**—that is to say, *pigment whose origin from the blood-coloring matter is certain*—is derived usually from blood which has escaped from the vessels or has undergone coagulation in the vessels, and consequently *depends upon local changes*. Occasionally, also, it may be traced to the absorption of hæmoglobin by the blood, or to changes in the blood as the result of which granular pigment or hæmoglobin gets into the plasma and when deposited gives rise to pigmentation of the tissue. Such deposits of blood-pigment have been called *hæmochromatoses* by von Recklinghausen.

Extravasations of blood quickly undergo changes which are visible even to the naked eye. In the skin they are at first brownish, then blue, green, and yellow. Where small hæmorrhages have occurred in the substance of a tissue, as in the peritoneum, pleura, or lung, reddish-brown or blackish spots will be visible long afterward. In bodies which are rapidly putrefying these areas may be slate-colored. Larger hæmorrhages into the tissues—for example, in the brain or in the lung—come to have a rusty color after a time, and still later the affected spot shows ochre-yellow, yellowish-brown, or brown pigmentation. Corresponding with all these changes in color are physical and chemical changes in the hæmoglobin and in the iron contained in it.

When **hæmorrhages** occur into the tissues or into any of the cavities of the body, a considerable quantity of the blood-plasma and of the corpuscles is taken up unchanged by the lymph-vessels in the neighborhood. Other red corpuscles seem to have the hæmoglobin dissolved out of them, leaving the colorless stroma. This dissolved *hæmoglobin* diffuses itself into the surrounding tissues and gives rise to the changes in color of the tissues in the neighborhood of the extravasation. Part of this dissolved coloring-matter may be eliminated in the urine in the form of *urobilin* (*urobilinuria*), but some of it is precipitated in the tissue in the form of granules and crystals. These latter are *yellowish-red or ruby-red rhombic plates and needles of hæmatoidin* (Fig. 81), and are a frequent residuum of hæmorrhages.

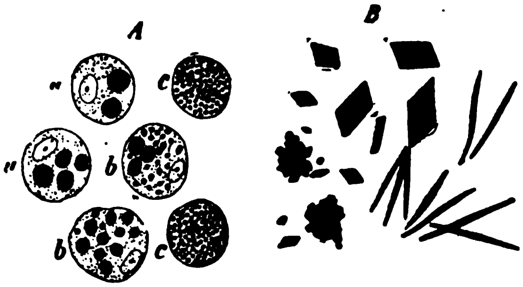

FIG. 81.—A, Cells containing amorphous blood-pigment; *a*, Those in which there are only a few larger fragments of red blood-corpuscles; *b*, *c*, Those in which these fragments are numerous, but quite small; B, Rhombic plates and needles of hæmatoidin. (Magnified 500 diameters.)

Part of the dissolved blood-pigment may be taken up by cells, in which it appears in the form of *yellow and brown pigment granules*. Still other blood-corpuscles disintegrate at the site of the hæmorrhage and

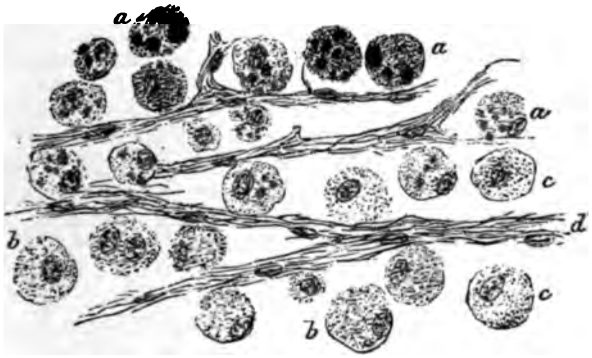

FIG. 82.—Cells containing hæmosiderin and hæmatoidin, from an old hæmorrhagic focus in the brain. *a*, Cells containing hæmosiderin; *b*, Cells containing hæmatoidin; *c*, Fat-granule cells which have become clear; *d*, Newly formed connective tissue. (Preparation hardened in alcohol and treated with potassic ferrocyanide, hydrochloric acid, and carmine. Magnified 300 diameters.)

form yellow and brown irregular masses. This is very frequent in large extravasations, in the so-called *hæmatomata*. Pigment derived in any of these ways from the blood is very frequently taken up by cells, and in this manner are formed the so-called *blood-corpuscle cells and pigment-carrying cells* (Fig. 81, A, and Fig. 82, *a*, *b*).

When red blood-corpuscles are just beginning to disintegrate, the coloring-matter found is hæmoglobin; but this is quickly changed, and the yellow and brown masses and granules found both in the cells and lying free in the tissue are, as a rule, **derivatives of hæmoglobin** and not hæmoglobin itself. These derivatives of hæmoglobin are divided into two groups according as they contain iron or not, the former being called *hæmosiderin*, the latter *hæmatoidin*.

Hæmatoidin, identical chemically with *bilirubin*, is a ruby-red or reddish-yellow pigment, which occurs either in crystalline form or as irregular granules, which may be quite amorphous or may be rather angular in shape, suggesting a rudimentary and imperfect crystalline form. It is soluble in chloroform, carbon disulphide, and absolute ether, but insoluble in water and alcohol. It would appear to be more abundant when the blood-pigment is not much exposed to the action of living cells, as in the centre of large extravasations and in hæmorrhages into preformed cavities of the body, as, for example, into the pelvis of the kidney or into the subdural space. It may be produced artificially by introducing blood in glass cells under the skin or into the peritoneal cavity in such a way that the body-fluids may have access to it.

Hæmatoidin is found both in the cells and loose in the tissue. When it is contained in cells it has usually got there as the result of phagocytosis, though occasionally, particularly in cartilage- and fat-cells, the hæmatoidin will have been absorbed while in solution, and have been deposited afterward in the solid form.

Hæmosiderin, the derivative of hæmoglobin containing *iron*, is met with in the tissues for the most part in the form of yellow, orange, or brown masses and granules, which deepen in color with time, and are usually contained in cells, sometimes in the very red corpuscles from which the hæmoglobin has been absorbed. When treated with potassium ferrocyanide and dilute hydrochloric acid, hæmosiderin becomes blue as the result of the formation of Prussian blue (Fig. 82, *a*); it becomes black when acted upon by sulphide of ammonium, iron sulphide being formed.

Hæmosiderin is formed, according to Neumann, more particularly when the extravasated blood, or that composing a thrombus in a vessel, is subjected to the action of the cells, and it is consequently more abundant in small extravasations and in the neighborhood of larger ones. The formation of hæmosiderin may take place in the cells or in the intercellular spaces. That which is found in the cells may have been formed from fragments of disintegrated blood-corpuscles which have been taken up by the cells, or from dissolved hæmoglobin which has infiltrated them, as is indicated by the occasional finding of both wandering and fixed cells whose bodies are stained diffusely yellow and which are stained blue by the Prussian-blue reaction. Furthermore, when hæmoglobin is excreted by the kidneys, iron-containing pigment frequently forms in the tubular epithelium; and cartilage-cells, which could hardly be supposed to act as phagocytes and take up solid fragments of blood-corpuscles, often contain granules of similar pigment, even when lying at some distance from a hæmorrhagic area.

The free pigment and the pigmented cells, then, cause distinct and early pigmentation of the tissue in the neighborhood of an area of extravasated blood. But soon the pigmented cells find their way into the lymph-channels and form *metastases* along the course of the lymphatics and in the adjoining lymph-nodes (Fig. 83), in which at first the pigment is lodged in the bodies of the free lymphoid cells, but later may come to lie in the tissue-cells also. After a time hæmosiderin is either destroyed and disappears, or changes into a pigment which no longer gives the reaction for iron.

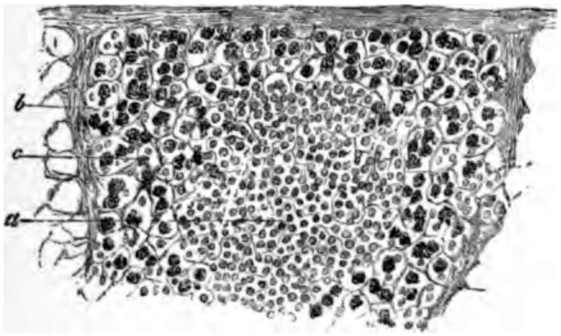

Fig. 83.—Accumulation of cells containing pigment granules in the lymph-glands after the absorption of an extravasation of blood. *a*, Peripheral nodule; *b*, Lymph-sinus; *c*, Cells containing pigment granules. (Preparation hardened in Müller's fluid, stained with carmine, and mounted in Canada balsam. Magnified 100 diameters.)

If hæmosiderin comes in contact after death with hydrogen sulphide it becomes black, and then causes the black and gray spots or diffuse patches spoken of as **pseudomelanosis.** This is observed most often in the intestine, in the peritoneum, and in suppurating wounds, since in these localities hydrogen sulphide is more apt to be formed in the course of putrefaction.

The question whether hæmosiderin granules may be converted into a pigment devoid of iron is differently answered by different authors. M. Schmidt and Neumann are of the opinion that the iron reaction of hæmosiderin is by no means constant, that it is quickly lost, and that it may even be absent from the first. The fact is that not infrequently the iron reaction is not obtained when the conditions are all such as to lead one to infer the presence of hæmosiderin. If the pigment in such cases is not hæmatoidin it must be supposed that the iron has disappeared from the hæmosiderin or has been converted into some form not sensitive to the Prussian-blue reaction, without thereby producing any change in form or color of the pigment.

Since the investigations of Vogel* the black pigment characteristic of *pseudomelanosis* has been believed by most authorities to be due to the formation of sulphide of iron as the result of the action of hydrogen sulphide upon the iron of the hæmoglobin. Perls † considers it to be sulphide of iron formed from the hæmatin of dissolved corpuscles, which results when simultaneously with the disintegration of the corpuscles hydrogen sulphide is formed in the course of putrefaction. Grohe ‡ believes that as a result of putrefaction the iron is liberated from its combination in the hæmoglobin, and that when thus freed it readily combines with the hydrogen sulphide present. E. Neumann, § however, is of the opinion that pseudomelanin is not a product of putrefactive processes alone, but that it depends to a large extent upon local conditions which bring about a deposit of iron-containing blood-pigment during life, and that this accumulated pigment is then later acted upon by the hydrogen sulphide of putrefaction. This view is supported by the fact that in pseudomelanosis almost all the black granules are contained in cells.

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* "Path. Anat.," i, p. 163.

† "Lehrbuch der allg. path. Anat.," i.

‡ *Virchow's Archiv*, 20. Bd.

§ Ibid., 111. Bd.

§ 75. **When large numbers of red blood-corpuscles break down in the blood,** hæmoglobin or methæmoglobin may come to be dissolved in the plasma, or portions of broken-down corpuscles may be swept about in the circulation. This condition is most pronounced in poisoning by arsenic, toluylendiamine, potassium chlorate, and mushrooms, though it is observed also in many infectious diseases, in malaria, and in pernicious anæmia. Dissolved hæmoglobin or methæmoglobin imparts a red color to the blood-plasma, and this condition is termed *hæmoglobinæmia*. When much dissolved hæmoglobin is contained in the blood a portion of it may be excreted by the kidneys, giving rise to *hæmoglobinuria* and *methæmoglobinuria*, in which case the urine is of a reddish color that varies from a light brownish red to a decidedly dark red. This is especially the case in arsenic-poisoning, but occurs occasionally as the result of other influences, as, for example, after exposure to cold (periodical hæmoglobinuria).

When the disintegration of the red corpuscles is not so complete, and fragments of them remain in the blood, as is the case not infrequently after burns, the fragments accumulate in the capillaries of the liver, spleen, lymph-nodes, and bone-marrow, and to a much less extent in some of the other organs. Sooner or later they are taken up by cells.

In the liver, as the result of this increased supply of hæmoglobin, there is considerable increase of functional activity, which is shown by the presence of an increased amount of bile-pigment in the bile, and occasionally oxyhæmoglobin also may be present in it (Stern). At times, when the amount of hæmoglobin brought to the liver is too great to be wholly disposed of in this way, one or other of the **derivatives of hæmoglobin may be deposited in the cells of the liver itself** or in other organs, or may be **eliminated by the kidneys.** When organs are colored yellow, orange, or brown as the result of such deposits, the condition has been aptly named by von Recklinghausen **hæmochromatosis.**

The derivatives of hæmoglobin deposited in this way are the same as those met with in other extravasations of blood, and consist partly of pigments free from iron and partly of hæmosiderin. The latter is a frequent cause of pigmentation of the tissues, and it is therefore permissible to speak of a *pigmentation by hæmatogenous siderosis*.

These **deposits of iron-containing pigment** are most often met with in the liver, where they occur as yellow granules or masses in leucocytes and endothelial cells, in the plasma of the capillaries, in the liver-cells, and

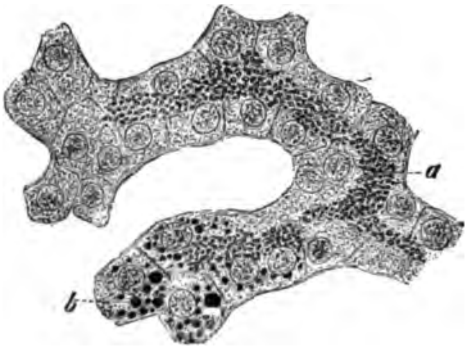

FIG. 84.—Infiltration of the trabeculæ of liver-cells with yellow hæmosiderin granules (as at *a*), from a case of pernicious anæmia. *b*, Cells in a condition of fatty degeneration. (Preparation treated with osmic acid and carmine, and mounted in glycerin. Magnified 250 diameters.)

in the star-cells of Kupffer (Fig. 84). In pernicious malaria and pernicious anæmia the majority of the liver-cells may contain such pigment, as the result of which the whole liver may have a brownish color.

When large quantities of broken-down corpuscles or of hæmoglobin derivatives are brought to the liver, they accumulate more especially at the periphery of the acini (Fig. 85, *d*, *e*), and in the periportal connective tissue, lying, as before stated, partly free in the capillaries, or in the tissues themselves, and partly inside of leucocytes, liver-cells, connective-tissue cells, and the endothelial cells of the capillaries. The tissues thus infiltrated present a reddish-brown coloration distinctly visible to the naked eye.

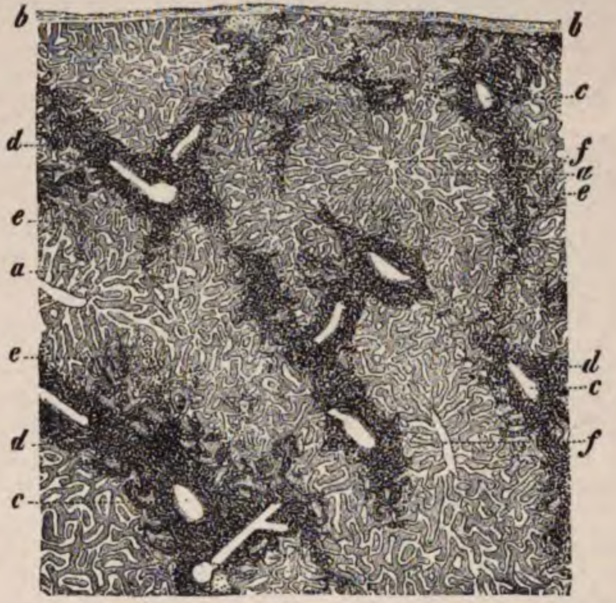

FIG. 85.—Hæmochromatosis of the liver, from a man who died of morbus maculosus Werlhofii. *a*, Acini; *b*, Peritoneum; *c*, *c*, Branches of the portal vein; *d*, Infiltrated periportal connective tissue; *e*, Pigment deposited inside of the capillaries of the hepatic lobules; *f*, Venulæ centrales. (Preparation hardened in alcohol, stained with carmine, and mounted in Canada balsam. Magnified 20 diameters.)

The pigment which is carried to the *spleen* is found for the most part in cells lying loosely in the pulp, at times also in the fixed cells of the tissue. In the *lymph-glands* it lies chiefly in cells within the lymph-channels. In the *bone-marrow*, where it is often present in large quantity, it is found in cells in the capillaries, in the capillary endothelium, and in the pulp-cells.

In the *kidneys* it is most abundant in the epithelium lining the convoluted tubes, but is also met with in the lumina of the tubules, in the capsular epithelium, and in the endothelium of the capillaries. When masses of hæmosiderin are present in the circulation they are almost certain to be found in the capillaries of the kidney. When hæmoglobin is being eliminated by the kidney it is usually to be found in the lumina of some of the tubules. When pigmentation of the kidney is extensive, it may often be detected with the naked eye.

A large part of the hæmosiderin which is found in the various organs has been brought to them in the form of granules or small masses, and is then, as a rule, contained in leucocytes in the capillaries. But, in addition to this, solid particles of pigment would also appear to be formed in the cells themselves from material brought to them in solution. This view is sustained by the fact that, in applying the Prussian-blue reaction for the detection of iron, many of the cells which contain no definite granules nevertheless stain diffusely blue, indicating the presence of iron diffused through their substance. The iron-containing pigment which thus infiltrates the cells would appear to be later excreted by them in the form of solid masses of pigment, though it is, of course, possible that some of this diffuse coloration may have resulted from the solution of the iron within the cells. It is also suggested by the observations of a number of investigators that colorless iron-containing material—albuminates, perhaps—may at times be present in cells in the body, since the iron reaction develops oftentimes many more iron-containing granules than were otherwise visible in the tissue.

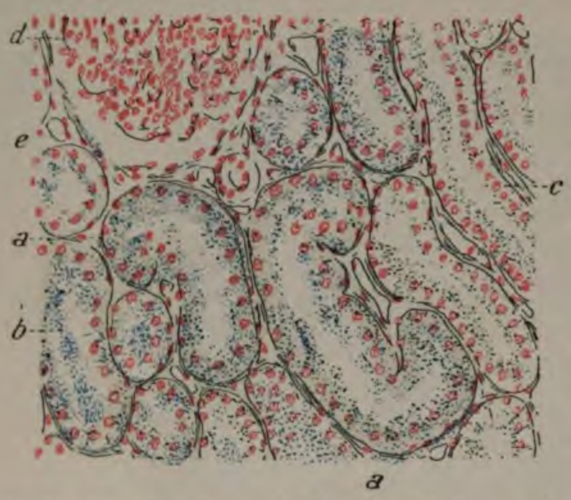

FIG. 86.—Hæmatogenous deposit of iron in the kidney, from a patient who died of pernicious malaria (contracted in Bagamayo). *a*, Convoluted uriniferous tubules, the lining epithelial cells of which contain granules of iron and are stained a pale-blue color; *b*, Iron granules in the lumen of the tubule; *c*, Straight uriniferous tubules; *d*, Glomerulus; *e*, Capsule epithelium, also containing iron granules. (Preparation hardened in alcohol, treated with alum carmine, potassic ferrocyanide, and hydrochloric acid, and mounted in Canada balsam. Magnified 150 diameters.)

The **deposit of iron-free pigments**, *hæmatoidin* or *bilirubin*, is usually very scanty in cases of hæmatogenous pigmentation, as the result of disintegration of blood-corpuscles in the circulation. Occasionally, however, pigment is met with in the various organs which fails to give the reaction for iron, and which it is reasonable to suppose has not contained iron at any time, though it should be remembered that after a time hæmosiderin fails to respond to this reaction.

Von Recklinghausen has applied the name *hæmofuscin* to a *form of pigment devoid of iron* which occurs as yellow granules in the heart-muscle and in smooth muscle-cells. It is occasionally so abundant in smooth muscle as to cause much swelling of the cells, and it is almost constantly present, according to Goebel, in some of the muscle-cells of the outer layer of the muscularis of the jejunum in persons who have passed their eighteenth year. This pigmentation increases with age, and may ultimately become so abundant as to impart to the intestine a distinctly yellow or brownish coloration. Similar pigment is also met with in the muscle-cells of blood-vessels and other muscular organs, in the cells of the connective-tissue sheaths of blood-vessels, and in the cells of gastric, intestinal, tear, sweat, and mucous glands. In the heart, pigmentation of the muscle-cells is of very frequent occurrence in old age, and is sometimes so marked in atrophic conditions of the heart as to cause distinct coloration of its muscle. Marked pigmentation also takes place in voluntary muscle-tissue when it undergoes atrophy, though it is by no means constantly present.

The nature and source of hæmofuscin are not determinable with certainty by microscopic examination, though von Recklinghausen and Goebel are both inclined to class the pigmentation caused by it among the hæmochromatoses.

It is uncertain whether the hæmoglobin or some other ingredient of the blood furnishes the material from which hæmofuscin is formed.

Experiments conducted in my laboratory by de Filippi show that iron preparations introduced into the system subcutaneously or by the intestine, in soluble form (Schmiedeberg's ferratin), find their way in considerable quantity into the fluids of the body and into the blood, and are deposited particularly in the bone-marrow, spleen, and lymph-glands. The iron may be demonstrated microchemically, lying in intercellular spaces in the form of fine granules or small masses, or in solution diffused through the cells and in the walls of the blood-vessels. In the liver the deposit is chiefly observed in leucocytes, endothelial cells, and Kupffer's stellate cells in the blood-vessels, while the liver-cells themselves, as a rule, contain iron only transitorily and in such a form as will permit us to detect it by microchemical means in only a few of the cells.

According to the researches of Biondi, which were also made in my laboratory, the conditions observed in chronic poisoning by toluylendiamine, which brings about progressive disintegration of the red blood-corpuscles, are very similar to those just narrated, for here also the places where the iron is deposited are the bone-marrow, the spleen, the lymph-glands, and the vascular and connective-tissue framework of the liver, while the liver-cells themselves remain free.

And, finally, a similar result is obtained when the ductus choledochus of animals is ligated, in which case iron-containing bile is forced to enter the blood.

In man such iron-containing pigment is almost constantly found inside of the cells of the organs in question, though in most cases in very small quantity. This iron is, on the whole, to be considered as having originated from broken-down red blood-corpuscles, though it is possible also that at times an excess of iron is taken into the system. Biondi is of the opinion that when, under pathological conditions, as is frequently the case, large amounts of iron are found not only in the connective-tissue cells of the above-mentioned organs, but in the liver-cells as well, the inference is justifiable that there has been both abnormal disintegration of the blood-corpuscles and at the same time derangement of the function of the liver. It would appear that healthy liver-cells limit their content of iron, giving up to the bile, to the blood, or to the lymph, any excess of it which may be brought to them, so that it is only exceptionally and then only for a short time that they contain any iron which may be detected by microchemical tests. Under pathological conditions this ability of the liver-cells to dispose of iron would appear to be impaired, as the result of which there occurs in them an excessive and persistent accumulation of iron.

It is probable that the iron which is deposited in the above-mentioned organs may later be of use in building up new tissue, more particularly in the elaboration of red blood-corpuscles.

In **malaria** two pigments result from the destruction of the red corpuscles by the micro-organisms of that disease. The one is formed by the plasmodia themselves. It is black, gives no iron reaction, and lies in the bodies of the plasmodia. Nothing is known as to its nature. The other is hæmosiderin, which passes into the plasma of the blood as the result of the destruction of the corpuscles, and is later deposited in the liver, spleen, and marrow of the bones. When excessive destruction of the blood occurs, it may also lead to a condition of siderosis of the kidneys (Fig. 86) and to elimination of iron in the urine.

The greenish coloration which is observed, in decomposing cadavers, in the neighborhood of blood-vessels filled with blood, is dependent upon the formation of sulphide of methæmoglobin through the action of the hydrogen sulphide upon the blood.

§ 76. A pathological pigmentation of the tissues by bile-pigment is designated **jaundice** or **icterus.** Icterus is a symptom which is frequently present in the course of a number of diseases of the liver, and is a frequent occurrence during the first few days of life (*icterus neonatorum*).

During life the pigmentation known as jaundice is apparent chiefly in the skin, conjunctivæ, and urine, but after death it may be detected also in the internal organs, the serous membranes, the lungs, kidneys, liver, in the subcutaneous and intermuscular connective tissue, in the blood-plasma, in clots in the vessels, etc. Fresh icteric colorations are yellow, but after a time the skin may assume an olive-green or dirty grayish-green color; and similar colorations are also met with in the internal organs, particularly in the liver and occasionally also in the kidneys.

Jaundice results from the entrance of bile or of bile-pigment (bilirubin) into the blood and liquids of the body. During its continuance the urine contains bile-pigment also. These biliary pigments have their origin in the liver, and jaundice is consequently a hepatogenous disease. It commonly depends upon some diseased condition of the biliary passages or of the liver itself, as the result of which the outflow of bile from the liver is impeded. The bile is then taken up by the lymphatics and blood-vessels. Such a condition may be brought about by catarrh of the bile-ducts; by narrowing or obliteration of the bile-ducts by cicatrices, by gall-stones, or by tumors which may have originated in the gall-ducts themselves or in the tissue in their neighborhood, and which compress them; by inflammatory conditions, abscesses, connective-tissue growths, tumors; or, finally, by congestion of the blood-vessels of the liver itself, which causes pressure upon or obliteration of the gall-ducts within the liver, and so prevents the outflow of bile through the gall-capillaries and smaller gall-ducts.

When for any reason the bile is congested in the small gall-ducts of the liver, the first thing which occurs, in all probability, is an absorption of a certain amount of the bile by the lymphatics of the liver. But as the process continues the bile accumulates more and more in the gall-capillaries and in the liver-cells themselves; the latter circumstance being due, doubtless, to the inability of the liver-cells to dispose of the bile which they have formed (Fig. 87, *a*). If the process continues for any considerable time the dilatation of the gall-capillaries may be very great (Fig. 87, *b*), so that ultimately they may burst and their contained bile may be discharged directly into the blood-capillaries (Fig. 87, *g*). Even in the early stages of jaundice, yellow (or green, in cases of sublimate fixation) granules may be seen in Kupffer's cells and in the endothelial cells of the capillaries, which often desquamate in consequence and lie free in the blood-vessels. Not infrequently such biliary congestion is followed by degenerative changes, necrosis, inflammation, and connective-tissue growth.

When bile-pigment, either still in solution or in the form of granules or small masses, finds its way into the blood in the manner above described, the tissues of the body, being bathed constantly by bile-stained lymph, gradually absorb some of the coloring-matter and are colored by it. Solid particles which may be circulating in the blood, for the most part in cells, slowly accumulate in the spleen and in the bone-marrow. After a time the bile-pigment in solution in the various liquids of the body becomes deposited as fine granules, or more rarely as rhombic or acicular crystals, which have already been described as hæmatoidin (Fig. 81). This crystalline deposit rarely occurs except in new-born infants, where the crystals form in fixed and wandering connective-tissue cells, in the liver-cells, and in the tubular epithelium of the kidneys. In intense icteric conditions very many of the cells of the body come to contain bile-pigment. This is often accumulated in large amount in the lymph-glands (Fig. 88), to which it is, as a rule, carried by cells, and whose lymph-channels may be so filled with the yellow granules as to give to the whole gland a yellowish-brown color.

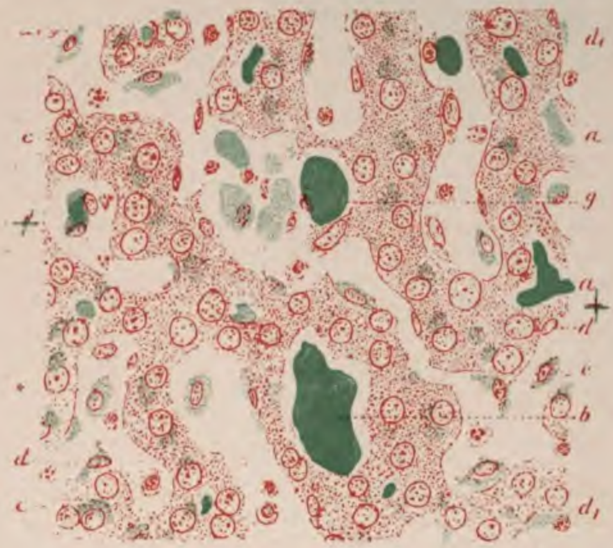

FIG. 87.—Icterus of the liver, from a case of cancer of the gall-bladder, in which there was compression of the ductus choledochus. *a*, Moderately dilated intravenous bile-ducts filled with bile; *b*, A large mass of bile-pigment in a widely dilated intravenous bile-duct; *c*, Bile-pigment in the liver-cells; *d*, d_1, Still firmly attached endothelial and Kupffer's cells, stained by granules of bile-pigment; *e*, Desquamated endothelial cells stained with bile; *f*, Portions of pigment surrounded by cells; *g*, Escape of pigment contained in the bile-ducts into a capillary. (Preparation hardened in corrosive sublimate, stained with alum carmine, and mounted in Canada balsam. Magnified 365 diameters.)

In the kidneys, which are active in eliminating the biliary pigment from the body in jaundice, there is also much pigmentation, particularly of the secreting epithelium of the tubules, which often desquamates in consequence (Fig. 89, *a*). When casts of the urinary tubules are formed

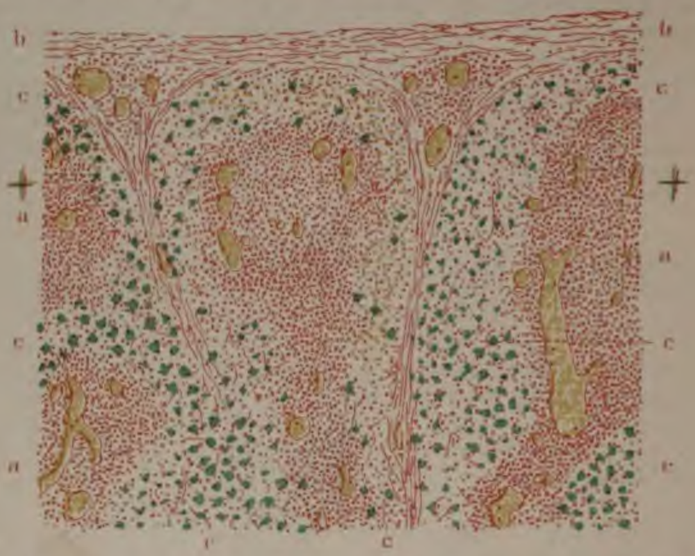

FIG. 88.—Icterus of the lymph-glands, following an attack of jaundice due to obstructed outflow of bile (Fig. 87). *a*, Lymph-follicles with distended blood-vessels; *b*, Capsule; *c*, Lymph-channels with cells which contain yellowish-green pigment granules (entirely free from iron). (Preparation hardened in corrosive sublimate, stained with carmine, and mounted in Canada balsam. Magnified 45 diameters.)

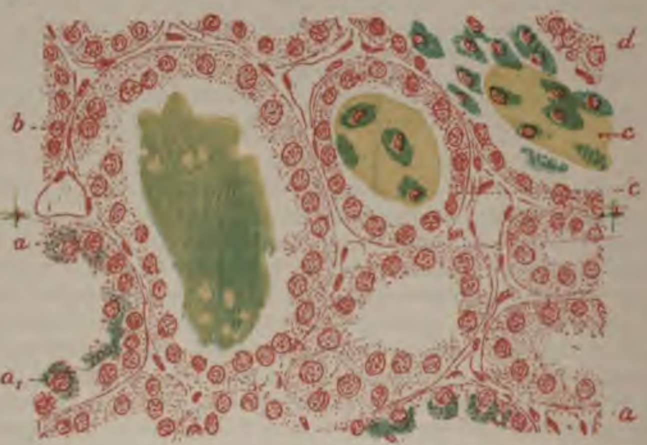

FIG. 89.—Icterus of the kidney, following an attack of jaundice due to obstructed outflow of bile (Fig. 87). *a*, Tubular epithelium containing yellowish-green granules; *b*, Large yellowish-green urinary cast; *c*, Cast with pigment-cells entangled in its substance; *d*, Desquamated epithelium containing bile-pigment granules. (Preparation hardened in corrosive sublimate, stained with carmine, and mounted in Canada balsam. Magnified 200 diameters.)

as the result of the degeneration of the tubular epithelium, these casts are usually colored by the bile-pigment (Fig. 89, *b*, *c*).

Associated with the deposits of bilirubin in jaundice, there is always more or less deposit of *hæmosiderin*, chiefly noticeable in the bone-marrow, in the spleen, and in the lymph-glands, occasionally also in the liver, so that the pigmentation of the tissues depends in part upon the presence of an iron-containing pigment in this condition also.

When unusual disintegration of red blood-corpuscles occurs within the blood, hæmatoidin or bilirubin is formed in association with hæmosiderin, as was explained in § 75, and is deposited in various parts of the body. Such extrahepatic bilirubin-formation is, however, very slight, and is never sufficient alone to cause jaundice, so that *a purely hæmatogenous icterus does not occur.* The liver is the great elaborator of bilirubin, and the production of this substance is at times increased in the liver as the result of disintegration of red corpuscles. *Jaundice, then, which follows breaking down of the blood, can only occur when associated with changes in the liver which result in the passage of bile into the blood.*

According to the majority of authors (cf. Harley), the bile, when obstructed in its outflow, finds entrance to the blood only through the lymph-channels; the chief reason for this opinion being that after ligation of the bile-ducts of animals jaundice does not occur unless the thoracic duct has also been ligated. Investigations which I have made on the livers of persons who have suffered from long-continued jaundice lead me to believe this opinion to be incorrect, and I believe that in all cases of chronic and well-marked obstruction of the outflow of bile there is also a direct entrance of the bile into the blood (Fig. 87), and that this depends upon inordinate dilatation and rupture of the intra-acinous gall-capillaries.

The question as to whether jaundice may be of hæmatogenous as well as hepatogenous origin has been under discussion and is still unsettled, notwithstanding numerous experimental investigations directed to its solution. Since, as a matter of fact, bilirubin may be formed in the tissues as the result of extravasation of blood, the likelihood of the occurrence of hæmatogenous icterus would *a priori* seem quite plausible. Experiments made with arsenious acid, toluylendiamine, and potassium chlorate, to determine the result of the disintegration of red blood-corpuscles in the blood, have, however, shown that the derivative of the blood which forms and is deposited in the various tissues is hæmosiderin, and that the formation of bilirubin under these circumstances is confined to the liver, which for the time being excretes an increased amount of intensely pigmented bile.

According to Minkowski and Naunyn, the urine of geese and ducks contains no bile-pigment after extirpation of the liver—a fact which would indicate that the transformation of blood-pigment into bile-pigment is ordinarily limited to the liver. The inhalation of vapor of arsenic for a very few minutes is sufficient to produce in geese intense polycholia and hæmaturia, the urine containing hæmoglobin in solution, fragments of red corpuscles, and biliverdin. If, now, the liver of such a goose be extirpated, biliverdin quickly ceases to be present in the urine, and there is, at the same time, no biliverdin in the blood. It is thus evident that in arsenic-poisoning the formation of the bile-pigment which appears in the urine must occur in the liver, in which broken-down blood-corpuscles are found in large numbers.

So far as may be inferred from the results of experiments which have been made up to the present time, it would seem that a purely hæmatogenous jaundice does not occur. The mere fact of the occurrence of jaundice in intoxications, after ether and chloroform inhalations, transfusion, snake-bite, and in septicæmia, typhoid fever, yellow fever, paroxysmal hæmoglobinuria, etc., is in no wise proof that the jaundice in these cases is of hæmatogenous origin. There is, indeed, in these conditions an increased destruction of red blood-corpuscles; but bilirubin is essentially a product of the liver, and its presence in the blood may readily be accounted for on the supposition that a part of the bile produced in excess in these conditions finds its way into the blood. In fact, Stadelmann has shown that change in the density of the bile may bring about its absorption by the blood.

Many theories have been proposed from time to time in explanation of *icterus neonatorum.* Frerichs believed it to be due to the passage of bile into the blood as the result of sudden diminution of intravascular tension in the liver after birth. Hofmeier supposes that the unusually large consumption of red corpuscles during the first few days of life leads to the production of a bile unusually rich in pigment, and that some of this bile finds its way into the blood. Birch-Hirschfeld believes that this benign type of jaundice, which is not traceable to septic infection and is not dependent upon serious anatomical changes in the liver, is produced by an œdematous condition of the connective tissue of Glisson's capsule, which condition is brought about by stasis in the area of distribution of the vena portæ and of what remains of the umbilical vein. Silbermann attributes it to congestion of bile dependent upon dilatation of the liver-capillaries and of the portal vessels immediately after birth, and he also believes it to be associated with a greater breaking down of red corpuscles. I myself would venture the opinion that the absorption of bile under these circumstances is referable not only to increased production of bile by the liver immediately after birth, but also to increased absorption of biliary coloring-matter from the meconium and its transportation to the liver.

According to E. Neumann, bilirubin crystals are frequently found in the fat-cells of the omentum, and at times also in the subserous fat, in the fat about the kidneys, beneath the pericardium, and in the mediastinum of new-born children, even when they are not jaundiced; and he explains this by supposing that after death the biliary coloring-matter which was in solution in the tissue-fluids has crystallized out. In both children and adults biliary coloring-matter which has found its way after death, by diffusion, into the tissue surrounding the gall-bladder may crystallize, more particularly in the fat-tissue.

§ 77. **Pigmentation of the tissues by foreign substances introduced into the body from without** occurs when substances possessed of color in themselves, and capable of resisting the action of the body-fluids, gain access in any manner to the tissues and remain there. The substances which may act in this way are naturally numerous, as are also the modes of their entrance into the body. *The lungs are their most frequent channel of entrance,* but they may also be taken in through the intestine or from wounds. *Tattooing of the skin* affords a familiar example of the introduction of pigment through wounds. This staining is effected by rubbing insoluble granular pigments, such as lampblack or cinnabar, into slight wounds of the skin. The pigments penetrate into the wounds and infiltrate the tissue in their immediate neighborhood, part of the pigment remaining there permanently, while some of it is carried to neighboring lymph-glands, which then participate in the pigmentation.

The lungs and their lymph-glands are often intensely pigmented as the result of inhalation of particles of dust, more particularly coal-dust, soot, iron-dust, etc. They may become actually black in consequence of inhalation of coal-dust. A part of the dust inhaled is carried to the bronchial lymph-glands, which often become quite black, and may undergo more or less softening when the pigmentation is excessive. When these glands are situated near blood-vessels, the latter may be secondarily involved in the pigmentation, and sometimes also in the softening, and in this way particles of the pigment may gain access to the circulation and may be carried to remote organs, such as the liver, spleen, and bone-marrow, where they may be deposited (cf. § 18).

Among the pigmentations which may result from absorption through the intestine we may mention the condition known as *argyria*, which is dependent upon the long-continued use of preparations of silver. The skin under these circumstances may assume an intense grayish-brown coloration, and in a similar way the internal organs may undergo pigmentation to a greater or less degree. The silver is deposited in the form of fine grains in the stroma of the tissues, more especially in the glomeruli and in the connective tissue of the medullary portion of the kidneys (Fig. 90, *b*), in the intima of the larger vessels, in the adventitia of the smaller arteries, in the neighborhood of mucous glands, in the papillæ of the skin, in the connective tissue of the intestinal villi, and in the choroid plexus of the lateral ventricles. Deposits may also occur in the serous membranes, but epithelial tissues, the brain, and the cerebral vessels escape. Extensive deposits in the medullary portion of the kidney may lead to growth of dense connective tissue, which then not infrequently undergoes calcification.

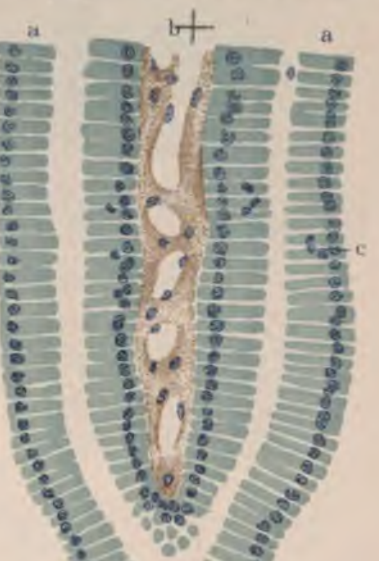

FIG. 90.—Deposits of silver in the pyramidal portion of a rabbit's kidney, after the animal had regularly received fixed doses of a silver-preparation for a period of seven months (experiment of von Kahlden). *a*, Epithelium of the collecting-tubes; *b*, Connective tissue filled with brown granules of silver. (Preparation hardened in alcohol, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 5[?] diameters.)

Iron particles taken into the body in large amount may also lead to pigmentation of the bone-marrow, spleen, and lymph-glands, though rarely to such an extent as to be visible to the unaided eye.

XIII. Cyst-formation.

§ 78. A **cyst** is a circumscribed cavity which is shut off from the surrounding tissues by a connective-tissue membrane or by tissue of complex structure, and whose contents are different from this capsule. When a cyst comprises only a single such cavity it is called a *simple cyst;* when it is divided into a number of compartments it is said to be *multilocular*.

The most frequent form of cyst is the so-called **retention cyst**, which results from the accumulation of secretion in a duct of a glandular organ, in the gland itself, or in any preëxistent canal. They all have an *epithelial* or *endothelial lining*.

These cysts form in organs provided with an open duct, when obliteration of this outlet occurs in any part of its course, provided that actively secreting parenchyma still exists beyond the point of obliteration. They are accordingly met with in the sebaceous glands of the skin, in the hair-follicles, in the uterine glands, in the mucous glands of the alimentary tract, in the epididymis (Fig. 91, *c*), in the urinary tubules, and less frequently in the gall-ducts and their glands, in the breast, in the pancreas (Fig. 92, *b*), in the glands of the mouth, etc. Larger canals may also become cystic—as, for example, the ureters, the vermiform appendix, and the Fallopian tubes (Fig. 93, *c*).

The obstruction of the duct necessary to cause a retention cyst may be brought about by accumulation of the secretion of the gland, or by cicatricial or neoplastic compression and consequent obliteration.

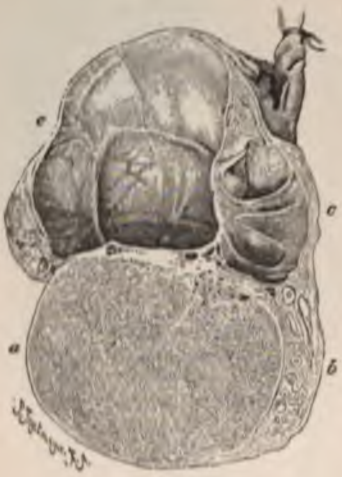

FIG. 91.—Section of the testicle and epididymis, showing multiple cysts in the head of the epididymis. *a*, Testicle; *b*, Epididymis; *c*, Cyst broken up into compartments. (Nearly natural size.)

Closed glandular cavities, such as the follicles of the thyroid gland, of the ovary, or of the parovarium, undergo cystic degeneration when their walls pour out an inordinate amount of secretion. Similarly, remains of fœtal canals or clefts—for example, those of the branchial clefts, of the urachus, or of Müller's ducts—may become cystic.

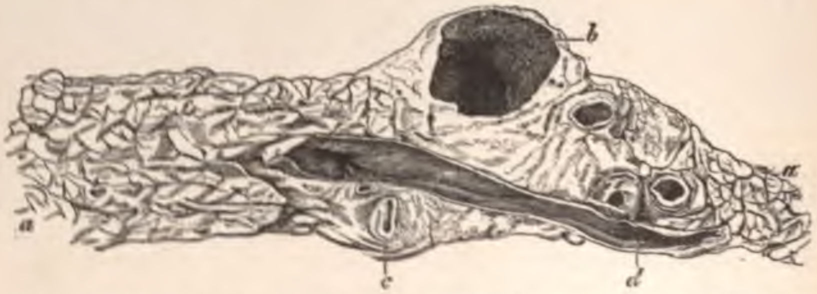

FIG. 92.—Cyst of the pancreas, caused by dilatation of a branch of Wirsung's duct. *a*, Glandular tissue; *b*, Cyst; *c*, Transverse section of an artery; *d*, Longitudinal section of a vein. (Natural size.)

Small cysts, such as are met with in mucous glands, vary in size up to that of a pea. Larger cysts, like those occurring in the liver and in the ovary, may attain the size of the fist or be even larger.

The contents of cysts depend upon the nature of the tissue in which they are formed. Thus cysts of the hair-follicles and of the sebaceous glands (*atheromata*) contain a semi-solid material, whitish, grayish, or brownish in color, composed chiefly of squamous epithelial cells, fat-globules, and cholesterin; cysts formed in mucous glands contain clear, or, when cellular elements are also present, milky, mucous liquid. When hæmorrhages take place into cystic cavities the blood imparts its color to the cyst-contents, making them red or brownish. Cystic Graafian follicles usually contain clear, more or less colored liquid; cysts of the thyroid gland and of the kidney contain colloid material, or clear, though occasionally cloudy, liquid.

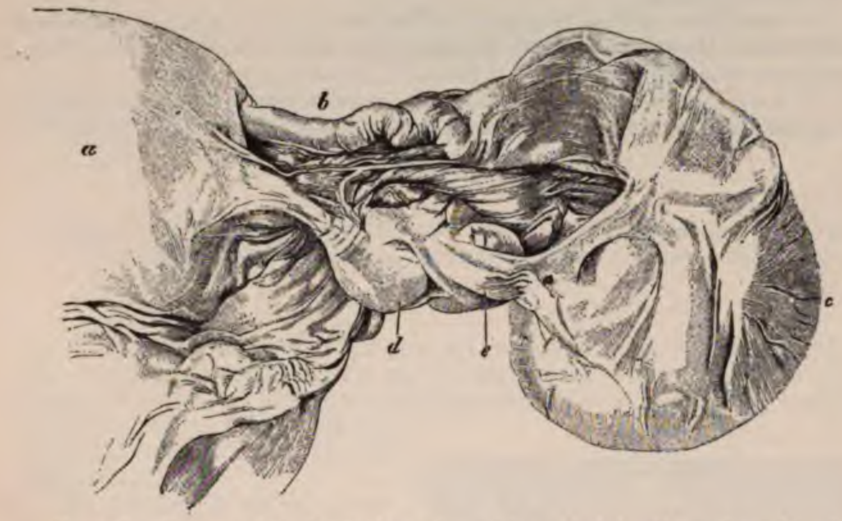

FIG. 93.—Dropsy of the Fallopian tube, with perisalpingitic and periovarian adhesions. *a*, Uterus; *b*, Uterine portion of the tube; *c*, Abdominal end of the tube, in a condition of cystic degeneration and adhering to the neighboring parts; *d*, Ovary; *e*, Membranous adhesion. (Two-thirds natural size.)

Retention cysts lined with endothelium may arise from blood-vessels, lymphatics, lymph-spaces, synovial membranes, or tendon-sheaths. Here also the nature of the cyst-contents depends upon its place of origin. Not infrequently the condition resulting in cyst-formation is caused by the shutting off of a portion of one of the cavities already named by a constriction.

As enlargement of a retention cyst goes on it is quite necessary that the tissue composing its wall should also develop, for otherwise defects in its wall would result. Cyst-formation is, therefore, not an exclusively degenerative process. The epithelial or endothelial cells lining the cyst-wall are the first to show this development, but the connective tissue upon which these cells rest participates in it also, as a rule, and may even, despite the stretching, become increased in thickness. It should further be stated that cyst-formation is very frequently associated with the *pathological development of new glandular tissue*, and constitutes, therefore, a secondary alteration in hypertrophic or tumor-like growths. Consequently it is sometimes impossible to distinguish between simple retention cysts of preëxistent gland-ducts and gland-vesicles, on the one hand, and those tumors, on the other, which are characterized by the presence of cyst-formations (the cystomata). Similarly, cysts lined with endothelium may originate from newly developed lymph spaces and ducts.

A second variety of cyst comprises the **cysts which result from degeneration, softening, and liquefaction of a portion of tissue.** Cysts are formed in this manner in the brain, in enlarged thyroid glands, and even in tumors. They are usually filled with either a clear or a more or less cloudy liquid.

A third kind of cyst results from the formation of a dense **capsule of connective tissue about any foreign substance** which may have found entrance into the body—as, for example, around a parasite.

A fourth variety of cyst is formed by **parasites** which pass through a cystic stage in the course of their development in the body.

SECTION V.

Hypertrophy and Regeneration of the Tissues and Organs.

I. General Considerations Concerning the Processes called Hypertrophy and Regeneration, and the Cellular Changes that Accompany Them.

§ 79. BY **hypertrophy** is meant an increase in the substance of a tissue or organ, brought about by an increase in or multiplication of its elements, in such a way that the structure of the hypertrophied tissue is similar to, or at least does not materially differ from, that of the normal.

By **regeneration** is meant the process by which a loss of substance in a tissue is restored by a new tissue that is exactly like that which was lost, or at least that contains the same elements which it had.

Hypertrophy may result from a morbid impulse existing in the germ-plasm itself, or from an impulse originating during the life of the individual. Regeneration, on the contrary, is always secondary to a tissue-lesion, which, however, may occur during either intra-uterine or extra-uterine life.

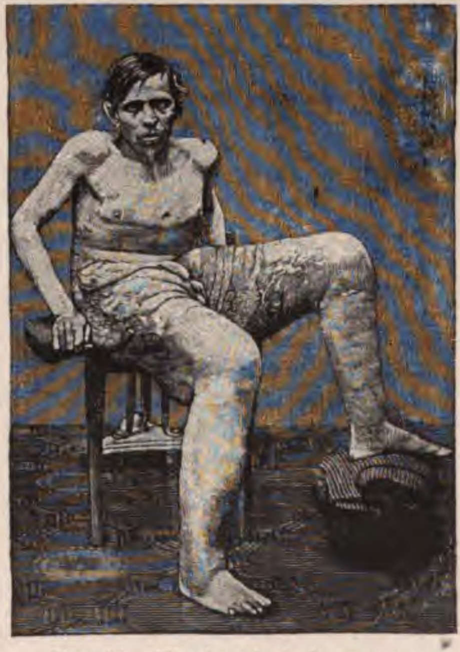

FIG. 94.—Elephantiasis femorum neuromatosa.

If an abnormal tissue-increase takes place during the period of embryonic development or of extra-uterine growth, and if there are no influences discoverable which would seem to account for the tissue-growth, then we are disposed to regard it as the result of **embryonic impulses**, and so we call it **hypertrophy of congenital origin.** If the enlargement affects the entire body—for example, if a newly born child weighs 5 or 6 kg., or if an individual reaches the height of 180 or 200 cm.

—this is called *general giant growth.* If the growth affects only certain parts of the body—for example, the entire head or one half of it, or one extremity, as a finger, or the labia majora or minora—it is called a *partial giant growth.* Hypertrophic growths of the skin that lead to changes suggesting the skin-formation of the pachydermata are called *elephantiasis* (Figs. 94 and 95).

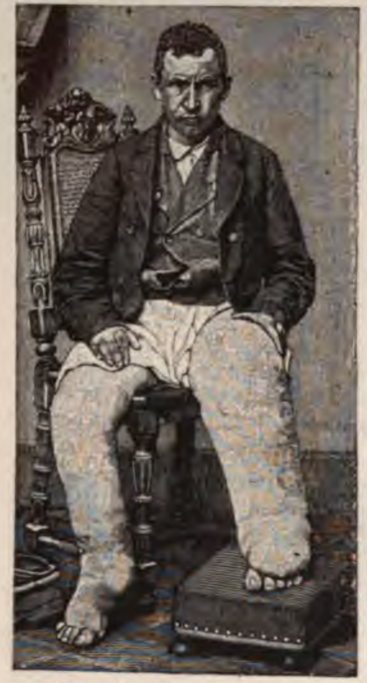

FIG. 95.—Elephantiasis cruris lymphangiectatica.

In hypertrophy of a limb or of a finger all the elements of the part are uniformly enlarged. In elephantiasis of the extremities the connective tissue of the skin and of the subcutaneous structures especially is apt to increase, though the development and structure of these growths show considerable variations in that the pathological new formation sometimes affects all the connective-tissue elements uniformly, sometimes single elements only—as, for example, the connective tissue of the nerves or the blood- or lymph-vessels—or at least takes its start from these. For this reason it has been customary to distinguish different varieties of elephantiasis, named, according to the structure of the hypertrophic tissue, elephantiasis neuromatosa (Fig. 94), angiomatosa, lymphangiectatica (Fig. 95), lipomatosa, etc.

To what extent it is possible to explain new growths by congenital impulse cannot be exactly determined, and in many cases it can be only surmised. In general the early appearance of the growth, as well as the history of heredity and the absence of possible external influences, speaks in favor of its congenital origin. Yet later influences which might bring about the growth do not disprove a congenital origin. For example, in the bones, especially of the head (Fig. 96), excessive bony growths occur whose beginning sometimes follows the operation of an external cause—as, for example, trauma or inflammation. Sometimes, on the contrary, it occurs without any such cause. Since in these cases, as we know by experience, the influences that determine the growth are not by themselves able to cause it, therefore we must explain the observed phenomena on the ground that the trauma, for instance, is merely the influence that starts up the new growth in a tissue already possessing congenital pathological impulses.

Very recently, under the titles of *akromegaly* (Marie), *pachyakria* (von Recklinghausen), and *ostéoarthropathie hypertrophiante* (Marie), there have been described certain peculiar enlargements of the tips of the extremities (Fig. 97), in some cases associated with enlargement of the face and with deformities of the spinal column. These cases had occurred for the most part in early or middle life, less often in later life, and had developed gradually.

So far as anatomical investigation (by Arnold, Marie, Marinesco, Thomson, Holsti) has been able to make out, the change consists in an increase in all the tissues that go to make up the extremities and the face. In this increase the bones also take part, in that they grow thicker (Fig. 98) and at the same time may be the seat of rounded or pointed exostoses. On the other hand, up to the present, an increase in the length of the bones has not been demonstrated in this disease (von Recklinghausen, Arnold), and so the term pachyakria of von Recklinghausen is fittingly chosen.

The cause and nature of these morbid phenomena are still obscure, and the above names are not used by all authors with the same significance. In Germany the term akromegaly is applied to all forms of enlargements of the ends of the limbs which lead to a paw-like appearance of the hands and a gigantesque appearance of the feet, while Marie, who first described these pathological manifestations, tries to draw a marked distinction between akromegaly and ostéoarthropathie hypertrophiante. He holds that in akromegaly the hands and feet are not deformed, but symmetrically enlarged, and, indeed, that the thickening and broadening diminish at the ends, so that the terminal phalanges are only slightly thickened. On the other hand, he holds that in ostéoarthropathie hypertrophiante the terminal phalanges are swollen so as to resemble drumsticks, and the articular ends of the bones are irregularly thickened. In the former case, moreover, the lower jaw is lengthened, in the latter case it is thickened. Marie believes that in many cases ostéoarthropathie hypertrophiante is a sequela of an inflammatory affection of the lungs and pleuræ. Accordingly he calls it ostéoarthropathie hypertrophiante pneumique, and he believes that the cause is to be found in a taking up of the toxic products of the body-fluids from the foci of inflammation in the lungs; so that the disease of the bones may be regarded as an infectious, toxic, hypertrophic inflammation.

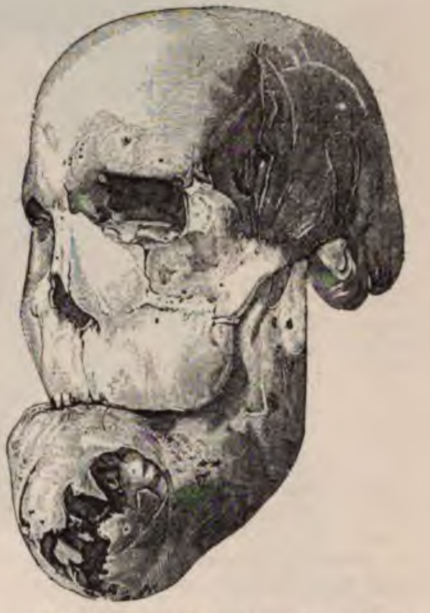

FIG. 96.—Leontiasis ossea, occurring in a boy the subject of general giant growth. (Observed by von Buhl.)

Some other authors regard akromegaly and ostéoarthopathie hypertrophiante as the result of a congenital predisposition (Virchow); others as the result of disturbances of the sexual organs (Freund); others as due to hypertrophy of the hypophysis (Henrot, Klebs) or to a persistence of the thymus gland (Erb, Klebs); still others believe them to be due to nervous influences (von Recklinghausen). Nevertheless none of these hypotheses is supported by anatomical and clinical observations. Finally, as a result of the investigations that have been made, it seems fair to assume that in the disease under consideration we have to do not with excessive growth that can be compared with the partial giant growths,

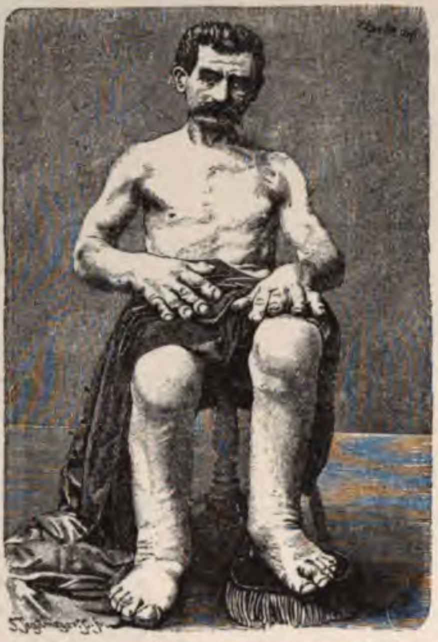

FIG. 97.—Akromegaly, according to Erb and Arnold. (Ostéoarthropathie, according to Marie and Souza-Leite.)

but with *acquired morbid conditions*, which develop either as independent diseases (akromegaly, pachyakria) or as secondary phenomena in the course of other diseases (ostéoarthropathie hypertrophiante pneumique).

The size of the entire body as well as of its separate parts and organs is subject to considerable variations within the normal physiological limits, according

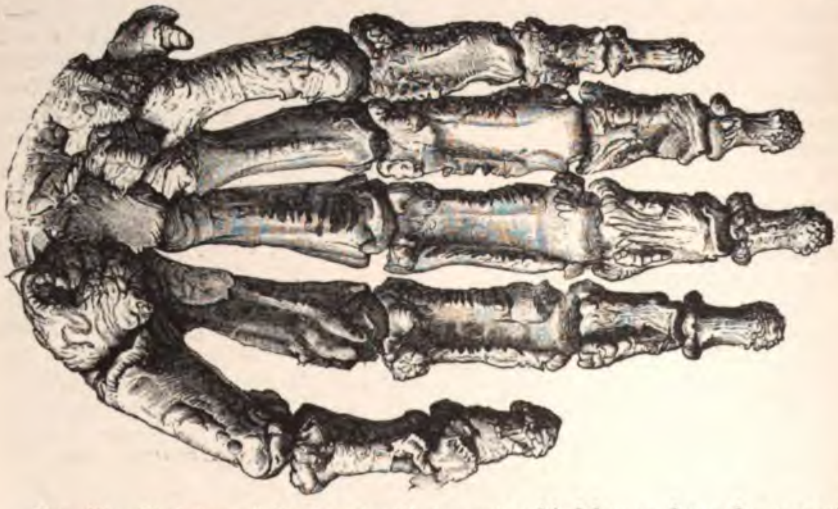

FIG. 98.—Skeleton of the hand with hypertrophied bones, from the case of akromegaly pictured in Fig. 97. (After Arnold.)

to race, family, and individual idiosyncrasy. The variation in the relation of the size of the separate parts and organs to that of the entire body is less great.

A most excellent compilation of statistics bearing upon this matter is given by Vierordt in his book[*] as well as in his article, which was published somewhat earlier.[†] I select from the first mentioned the following data:

The average height of well-built individuals is, men 172 cm., women 160 cm.; of the newly born, males 47.4, females 46.75 cm. The average body-weight in Europe is for man 65 kg., for woman 55 kg., for the newly born 3250 grammes.

The average weight of organs is as follows, the figures in parentheses being for the newly born: brain, 1397 (385) grammes; heart, 304 (24); lungs, 1172 (58); liver, 1612 (118); spleen, 201 (11.1); right kidney, 131; left kidney, 150; both kidneys, 299 (23.6); testicles, 48 (0.8); muscles, 29,880 (625); skeleton, 11,560 (445) grammes. Expressed in percentages of the body-weight we have the following figures, those in parentheses being for the newly born: heart, 0.52 (0.89); kidneys, 0.48 (0.88); lungs, 2.01 (2.16); stomach and intestinal canal, 2.34 (2.53); spleen, 0.346 (0.41); liver, 2.77 (4.39); brain, 2.37 (14.34); suprarenal bodies, 0.014 (0.31); thymus, 0.0086 (0.54); skeleton, 15.35 (16.7); muscles, 43.09 (23.4).

The phenomena that have been described under the names ostéoarthropathie hypertrophiante and akromegaly and pachyakria are clearly enough not a single disease. In one set of cases we have to do with a series of clinical symptoms that occur in the course of infections, such as tuberculosis and syphilis; while in another set of cases the etiology is unknown. It is a cryptogenetic disease. An excellent survey of the present status of the question is given in the works of Arnold.

For the further consideration of general and partial giant growth and elephantiasis, see the chapter upon Single Malformations in Section VIII., as well as the chapters upon the Pathological Anatomy of the Skin and the Bones.

§ 80. As has already been said in § 79, the **hypertrophies that are the outcome of congenital impulses**, and which occur without any discoverable cause, may affect not only whole sections of the body or entire organs, but, starting in some single tissue-elements, may limit themselves to one or two kinds of tissues. This is manifested in an especially striking way in the affection which is called *ichthyosis*, a peculiar anomaly of the epidermis in which the horny layers show a more or less marked hypertrophy.

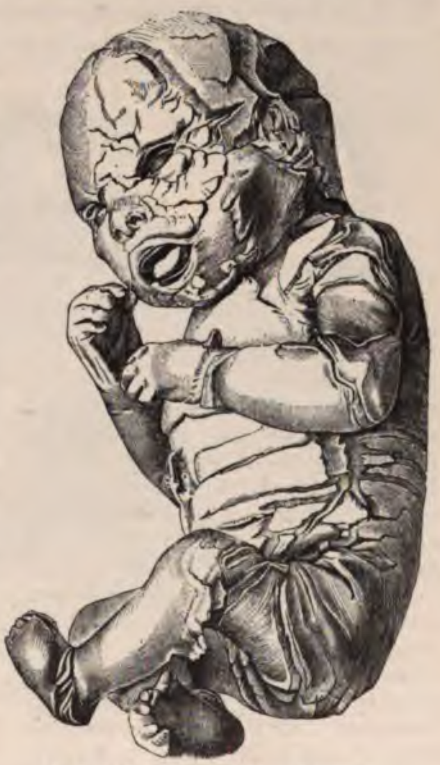

FIG. 99.—Ichthyosis congenita.

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[*] Entitled "Anatomische, physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediciner," Jena, 1893.

[†] "Das Massenwachsthum der Körperorgane des Menschen," *Arch. f. Anat. u. Phys.*, 1890.

In the form known as *ichthyosis congenita* one finds even in the newly born a similar increase in the horny layer, and cases occur in which the whole surface of the body (Fig. 99) is covered with thick plates of horn, separated from one another by cracks and fissures. These plates consist of scales and lamellæ which are pierced by the hairs, generally in an oblique direction, and they result from an increase in the normal epithelial processes of the skin.

In other cases, at a later period—for instance, during the first year of life—circumscribed areas of thickening of the epidermis develop, which form firm scales and plates, sometimes smaller, sometimes larger, giving the skin a rough or checkered appearance. The corium and the papillary layer generally are not involved in the ichthyosis. Nevertheless there are cases in which, in the areas of ichthyosis, the papillary layer is hypertrophied, and in these cases the roughness of the surface is intensified (*ichthyosis hystrix*). If the change is confined to small, limited spots, then circumscribed warts with rough epithelial covering are formed, and these may be called *ichthyotic warts*. In rare cases there are developed still more extensive layers of epithelium over the hypertrophied papillæ, whose scales are arranged perpendicularly to the layers of the skin; and these sometimes reach such dimensions that they are called *epidermal horns* (Figs. 100 and 101).

Fig. 100.

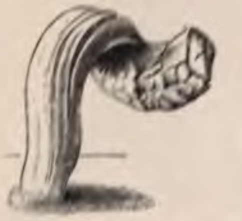

Fig. 101.

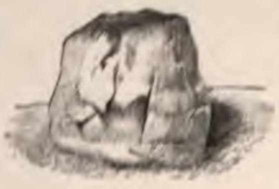

FIG. 100.—Cornu cutaneum, removed from back of hand. (Natural size.)

FIG. 101.—Cornu cutaneum, removed from arm. (Natural size.)

In very rare cases hypertrophic epithelial growths without known cause occur on the surface of the mucous membrane of the mouth, and there is a peculiar disease known as *black hairy tongue*, which is characterized by the formation of a black or brown epithelial growth over the papillæ filiformes.

By the hypertrophic development of hair in situations where only woolly hair, or even no permanent hair at all, should occur, there is brought about an abnormal hairiness over a larger or smaller area of the body, which is known as *hypertrichosis*, and this is explained either as a persistence or abnormal development of the primary or down-like hairs, or as a pathological development of the secondary hairs. Excessive growth

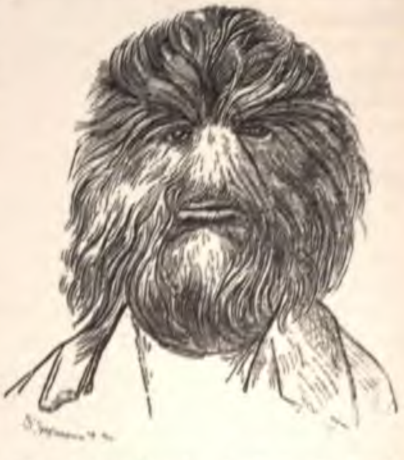

FIG. 102.—Head of a hairy individual, a woman. (From Hebra.)

of the nails leads to their pathological overgrowth, to *hyperonychia*, which is often followed by *onychogryphosis*, or claw-like deformities of the nails. It must, however, be noted that pathological increase of the nails is generally an acquired disease.

An *abnormal overgrowth of the internal organs* is of very rare occurrence, and is to be regarded really as an anomaly of growth and not as the result of intra-uterine influences, and it generally is so limited that we may class it among the individual variations in regard to extent of development. The brain and spinal cord are the commonest seat of such pathological enlargement, and it consists, as far as we know, in an increase sometimes of all the elements of the organs, sometimes only of certain of the tissue-elements.

§ 81. **Hypertrophies of the tissues from causes operating during extra-uterine life** are brought about most often by an increase in the work that the tissues and organs are called upon to do; but they may result, too, from other causes.

Hypertrophy from overwork is oftenest met with *in muscles* and *in glands*, but may occur in other structures. If the heart is called upon to do an extra amount of work, by reason of special valvular or aortic conditions, and if these conditions exist for a considerable length of time, then that part of the heart-muscle upon which this extra work falls suffers a more or less marked hypertrophy, and in this way the total bulk of the organ may reach double the normal, or even more.

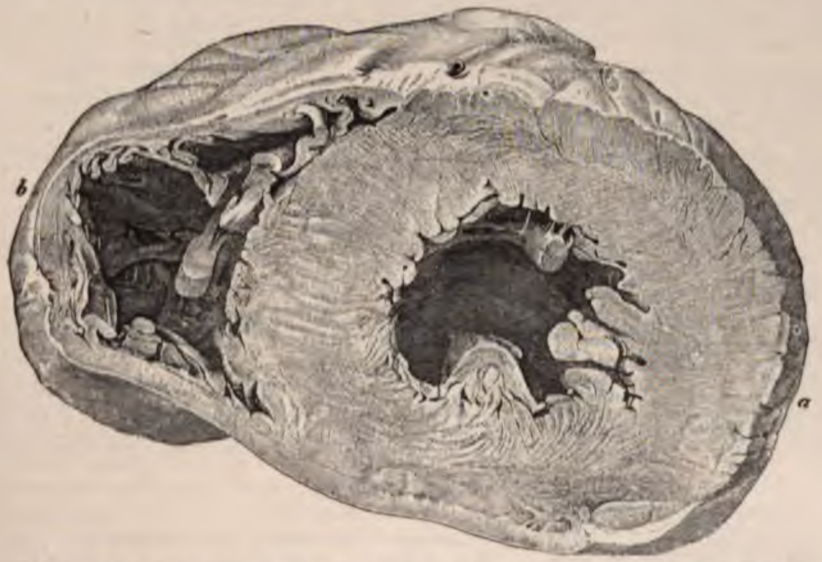

FIG. 103.—Transverse section of a heart, with hypertrophy of the left ventricle in insufficiency and stenosis of the aortic valves. *a*, Left ventricle; *b*, Right ventricle. (Natural size.)

Similarly, striated muscle, also the muscular layers of the bladder, the ureters, the uterus, the intestine, and the blood-vessels, may become hypertrophied from a persistent increase in their activity.

Of the glands, it is *the kidneys* and *the liver* especially that are capable of changing their size to suit functional needs, and correspondingly it is these glands that are most liable to undergo hypertrophy. If one kidney becomes destroyed, the other is capable of undergoing such an enlargement that it may reach approximately the same weight that the two kidneys together originally had. In the same way, the liver, after destruction of part of its parenchyma by disease, is capable of compensating for its loss by a hypertrophy of the remainder. This advantageous increase is called **compensatory hypertrophy**, because by it the normal function of the organ is restored. One may apply the same term also to muscle-hypertrophy, if by means of it lost function is restored. In the case of some other glands, as the salivary glands, ovaries, testicles, and mammæ, compensatory hypertrophy either does not occur at all or takes place only under special circumstances, as, for instance, when from loss of one part of the gland the work of the rest is increased. For example, it is possible that, in the case of a nursing woman who has lost one mamma, the greater demands made upon the other may result in an increase in its activity and a greater development of its secreting parenchyma. However, the loss of one ovary or testicle in adult life can hardly result in an increased activity or hypertrophy of the remaining one. In the case of the thyroid gland, extirpation of the larger part of it is generally not followed by any material hypertrophy of the piece remaining. On the other hand, the hypophysis suffers an enlargement which must be regarded as compensatory. In the case of the lungs, an increase in the activity of one portion, after loss or destruction of other parts, is generally followed only by a permanent distention, which, indeed, may even go on to atrophy. On the contrary, if during embryo life a faulty development of one lung takes place, the other may become the seat of a compensatory growth; and in the case of total failure of one lung to develop, this enlargement of the other may reach a very marked extent. Other tissues also behave in a similar way, and it may be stated as a general rule that compensatory development of a tissue is more nearly complete the younger the individual is. In the same way, compensatory development of the kidneys is more marked in young than in old persons. In the case of the brain, a compensatory growth of one part, after loss of another, is possible only during the developmental period.

In tissues that are in constant use a **lessening wear** may lead to hypertrophy. For instance, a diminished desquamation of the epidermal layer of the skin leads to a pathological thickening of it. If the incisor teeth of rodents are no longer normally worn down, by reason of the destruction of an opposing tooth or the oblique position of the teeth, they may grow to be very long and curved (Fig. 104). In the same way, finger- or toe-nails may reach an abnormal size, by reason either of absence of wear or of their being left uncut. Organs which undergo a temporary enlargement and then again become smaller may l

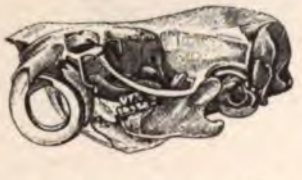

FIG. 104.—Hypertrophy of incisor tooth of a white rat, occurring by reason of oblique position of the jaw. (Natural size.)

hypertrophied from a **failure to diminish in size** after the natural increase. For example, the uterus, after pregnancy, may remain abnormally large, from involution failing to take place. Under some circumstances the **removal of a normal pressure from a tissue** may result in a new growth of tissue. For instance, the inner layer of the skull becomes thicker when the brain atrophies in early life or fails to develop. In atrophy of the kidneys a hypertrophy of the surrounding fat frequently takes place.

Among the commonest causes of pathological new growth are **frequently repeated** or **persistent irritations of the tissues**, of mechanical or chemical nature, associated with disturbances of circulation. Consequently these may be regarded as belonging to the chronic inflammatory processes (cf. chapter on Chronic Inflammations).

For example, frequently repeated mechanical irritation of the skin may lead to the condition called callous formation or corns, a condition which is characterized by massive thickening of the epidermal layer of the skin, partly also by pathological changes in the papillary layer and the corium. The frequently repeated inspiration of dust may result in a development of connective tissue in the lungs, and the irritation which the gonorrhœal secretion from the urethra brings about may lead to a growth of the papillæ of the epidermis in the neighborhood, and so to the appearance known as condylomata. Frequently recurring inflammation involving considerable areas of skin often leads to thickening of the nature of elephantiasis, and ichthyotic hypertrophy of the epidermis may result from the same cause. Epithelial tissues and also connective tissues may develop hypertrophic growths by the influence of bacteria which grow in them and produce there certain chemical products—for example, tubercle-bacilli and actinomycosis.

In many cases hypertrophic new growths are developed without our being able to discover any cause for them, and where we cannot assume a congenital impulse. For example, extensive hypertrophy of the lymph-glands occurs, and also of the other lymphadenoid structures, as the spleen, the cause of which is entirely unknown to us. In the same way we are ignorant of the cause of the very common hypertrophy of the thyroid gland, and must turn to hypotheses to explain the condition.

§ 82. If an organ is the seat of a hyperplasia it frequently is the case that **all parts of it do not take equal part in the hyperplasia.** For example, if a gland is enlarged, we find that in one case this is the result of an increase in the gland-substance proper; in another, of an increase in the connective tissue. In the first case we should call it a glandular, in the second a fibrous hyperplasia. Other organs also, made up of different tissues, behave in a like way. The inequality in the relation of the two tissues to each other may go so far that while the one is markedly hypertrophied, the other not only may not be increased, but, indeed, may even be atrophied. In this latter case it is for the most part the specific tissue-elements that atrophy, such as ganglion-cells, nerves, gland-cells, muscles, etc., while the connective-tissue elements are increased. The chronic inflammations are a very common cause of such a **localized hyperplasia of connective tissue** (see chapter on this subject). They play an important part in pathology, and only too often hyperplasia of the connective tissue, with atrophy of the parenchyma, follows in their train.

The same rule holds for regeneration as for hyperplasia. If a part of a tissue is destroyed, the **regeneration** which ensues **is often incomplete.** The capacity for regeneration which the tissues and organs of the human organism possess is limited. Large pieces of tissue which are lost cannot be restored—as, for example, an extremity, a finger, or a piece of brain. The highly organized tissues, and especially their specific elements, possess only a slight capacity for regeneration. Ganglion-cells, for example, probably never are regenerated in adults, and glandular epithelium only if the loss is slight, and if within the tissue (gland sacs or tubes) gland-cells still remain intact. If an injury has happened to a gland, and in consequence its continuity is broken, the wound is repaired not by gland-tissue, but by connective tissue, a pathological process that is called **cicatrization.**

The epithelium of the skin and of the mouths of glands has more capacity for repair than the glandular epithelium itself and ganglion-cells, for it is capable of being regenerated to a very considerable extent. Of all the connective-tissue structures, the periosteum especially is distinguished by its great power of regeneration, while cartilage shows but little of this power.

If from some embryonic impulse a tissue is produced the elements of which are in themselves normal, but do not correspond to the structure of the mother-tissue, it is called a **heteroplasia.** In this sense a cicatrix in an organ—for example, in the liver—is a heteroplasia—a term that one employs to indicate that in the area in question connective tissue is present, together with undeveloped epithelial elements, and not true liver-tissue. Even in relation to the connective tissue of the liver we may still call it heteroplasia, inasmuch as it materially differs in structure from the normal connective tissue of the organ. The same thing holds good for connective-tissue hyperplasia of the organs generally, especially for that which develops after inflammation. In consideration, however, of the close relationship of the tissues to one another, it is generally not reckoned among the heteroplastic tissue-growths.

The **tumors** *are the real type of heteroplastic growths.* They represent new growths, which, while they may resemble the mother-tissue upon which they grow, nevertheless possess peculiarities which distinguish them from the tissue upon which they are developed, and justify us in regarding the tumor as a heteroplastic structure.

§ 83. **Changes in the cells themselves are always the initial phenomenon of hypertrophy and regeneration,** changes which lead first to **enlargement of the cells** and then to **multiplication** of them. In the further development of the new growth **the basement substance formed by the cells may be increased.**

In *hypertrophy* the increase may be due entirely to enlargement of the cells, or there may be at the same time a multiplication of them; and accordingly a distinction is made between *simple hypertrophy*, or hypertrophy in the narrower sense, and a *numerical hypertrophy*, or *hyperplasia.* For instance, a muscular organ, such as the uterus or heart, may materially increase in size simply from enlargement of its muscle-cells. Moreover, in glandular hypertrophy an increase in size may occur in the same way from enlargement of the cells; though in these cases, if the hypertrophy is of considerable extent, there always occurs in addition a new cell-formation, so that the process has to be called a hyperplasia in the histological sense.

Under special circumstances *regeneration* also may consist of *simple enlargement of preëxisting cells*, or of *restitution of parts of cells that have been lost* (regeneration of axis-cylinder processes of ganglion-cells). In the case of a loss of considerable portions of a tissue there always occurs a *multiplication of the cells by division*, in addition to enlargement of them.

Cell-division leading to a formation of new tissue is always *characterized by peculiar preliminary changes in the nuclei and protoplasm;* that is, peculiar changes take place in the nuclei which enable us to predict the coming division of nucleus and cell, even in its preliminary stages.

The **completely developed nucleus** of a cell possesses a *peculiar structure* which may be clearly made out on microscopic examination with a high power, and after the proper manipulation. A **nucleus at rest** consists of an outer shell, or *membrane*, and the *nuclear contents*. This latter seems to consist of two parts: one a denser, more highly refracting nuclear substance, the other the nuclear fluid. The *nuclear fluid* forms a colorless mass, and is also spoken of as the *intermediate substance*. To the *nuclear substance* belong, in the first place, the *nuclear corpuscles;* in the second place, scattered *granules* and *threads*, which often form a *framework* (Fig. 105) which is clearly visible after proper treatment, and may be stained by the agents which color nuclei.

The **nuclear framework** is that part of the nucleus which undergoes a **series of typical changes of form** in the **subdivision of the nucleus**—changes which result in the separation of the nucleus into two masses of equal size. The process of nuclear division is often called **karyokinesis** (*καρυον*, kernel of a nut; *κίνησις*, movement), referring to these changes of form. Flemming, having in mind the skein-like structure of the nucleus when in process of division, has given to it the name **mitosis** or **karyomitosis** (*μίτος*, thread). The solid substance of the nucleus, which is colored by nuclear-staining dyes, is called **nuclein** or **chromatin** (Flemming).

If one studies the process of division of nucleus and cell in men or in other mammals, one is able to appreciate a series of preliminary phenomena in the nucleus at the commencement of division, which consist essentially of an increase of the chromatin, the substance which takes up the dye.

In many nuclei the chromatin forms granules or lumps of various sizes (Fig. 106), which arrange themselves in a net-like framework. In other cases the chromatin is distributed throughout the nucleus uniformly in masses of about equal size (Fig. 107). In still others the small granules are arranged in waving rows (Fig. 108). It is probable that the uniform distribution of the chromatin particles precedes the heaping up of the lumps and granules in the framework, and is followed by the formation of the rows of granules.

In the further course of the mitosis there are formed, in the next place, smooth, dense threads which stain darkly, and which are arranged in the form of *a mass of interlacing fine threads* (Figs. 109 and 110). Up to this time the nucleolus is still visible (Figs. 105 to 109). Now, however, it disappears (Fig. 110) and probably takes part in the formation of the mass of threads. At the same time the membrane loses its capacity for being stained (Figs. 109 and 110), and later on it disappears entirely.

By reason of the threads growing shorter and thicker, the *knotted mass of fine threads* (Figs. 109 and 110) develops into one of coarser threads, whose elements subdivide (Fig. 111) later on into separate portions which are called *nuclear segments* (Hertwig) or *chromosomes* (Waldeyer). Since the latter arrange themselves in the equatorial portions of the nucleus with their angles pointed toward the centre, there appears, if one looks at it from the pole (Figs. 105 to 120), a figure like a wreath, and later on star-shaped, and which is called the *mother-star* (Figs. 113 and 114).

Fig. 105.

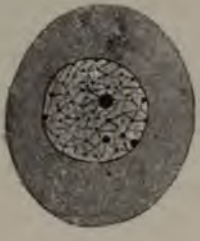

Fig. 106.

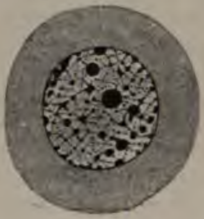

Fig. 107.

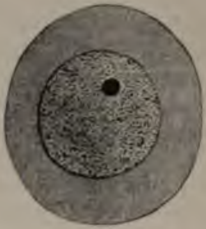

Fig. 108.

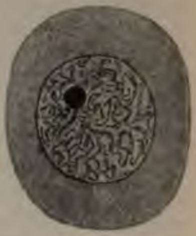

Fig. 109.

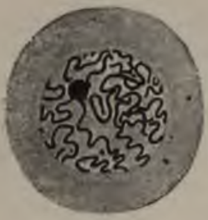

Fig. 110.

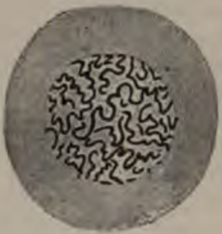

Fig. 111.

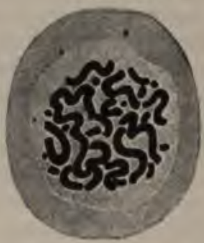

Fig. 112.

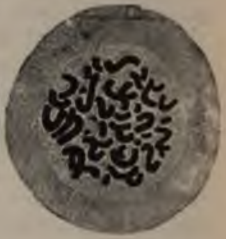

Fig. 113.

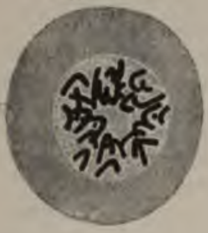

Fig. 114.

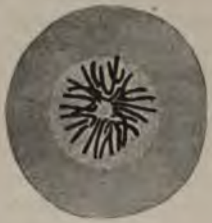

Fig. 115.

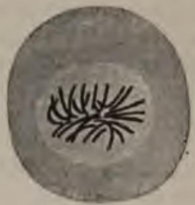

Fig. 116.

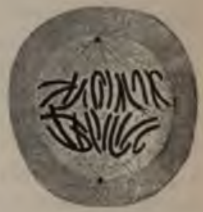

Fig. 117.

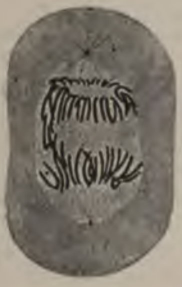

Fig. 118.

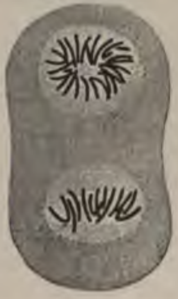

Fig. 119.

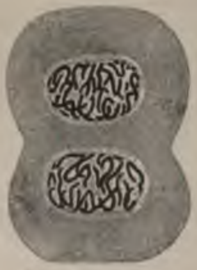

Fig. 120.

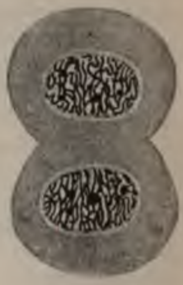

Fig. 105.—Nucleus at rest. Fig. 106.—Nucleus magnified; increase in the chromatin. Fig. 107.—Nucleus with evenly divided, finely granular chromatin. Fig. 108.—Nucleus whose chromatin granules are arranged in rows. Fig. 109.—Fine close skein, nucleolus and nuclear membrane persisting. Fig. 110.—Fine close skein whose granules have disappeared. Fig. 111.—Thick open skein; nuclear membrane gone. Fig. 112.—Segmented skein; nuclear threads divided into bent portions, without any special arrangement. Fig. 113.—Mother-star in process of formation; polar view. The threads are arranged with their angles pointed inward around a centre. (Also known as wreath form.) Fig. 114.—Completely developed mother-star; polar view. Fig. 115.—Mother-star; equatorial view. Fig. 116.—Stage of metakinesis; single loops visible, whose angles are pointed to the pole. Delicate spindle-figure in interior of nucleus. Fig. 117.—Daughter-star; side view (nucleus barrel-shaped). Spindle-figure in nucleus, and radial arrangement of protoplasm. Fig. 118.—Daughter-star separated; above, polar view; below, side view. Fig. 119.—Daughter-skein with thick threads; delicate new nuclear membrane; beginning of cell-division. Fig. 120.—Daughter-skein with fine threads (above), and framework form of the daughter-nucleus (below); cell-protoplasm in the act of dividing.

Viewing it from the side (Fig. 115), one sees that the segments of the nuclear threads have grouped themselves together in the equatorial plane of the nucleus.

Sometimes earlier, sometimes later, *two poles* become visible in the interior of the cell—that is, two extremely small spheres known as *polar corpuscles* or *central corpuscles*, or *centrosomes*. They lie at first close together, then later on separate from each other and act as centres, about which the nuclear elements group themselves. Between them is developed the *nuclear spindle* (Figs. 116 and 117), which consists of fine fibres which do not stain with nuclear dyes and which converge at the polar corpuscles. In the neighborhood of the polar corpuscles themselves the granules of protoplasm show a radial arrangement, so that figures are produced (Fig. 117) which are called *rays* or *stars* or *attraction-spheres*. In the next following stage of division of the nucleus, called *metakinesis*, a movement takes place among the chromosomes leading to the formation of V-shaped figures with their angles pointed toward the pole. Next, two star-shaped figures called *daughter-stars* are formed by the movement of the V's toward the poles following the arrangement of the spindle-fibres (Figs. 117 and 118).

Viewed from the pole (Fig. 118, above), the resemblance to a star is plain. Looked at from the side, it is barrel-shaped, and was formerly called the *barrel-figure* (Fig. 117). From the starlike figure of the daughter-nucleus there is developed later on a skein, first with coarse filaments (Fig. 119), then with fine (Fig. 120), which then changes to a figure like a network (Fig. 120). In the last stages of the phenomena that precede cell-division a new nuclear membrane is formed.

The **division of the cell** consists in a constriction of the protoplasm, which takes place during the last stages of the formation of the nucleus.

The phenomena of nucleus-division in the Mammalia cannot be clearly made out in all stages in detail, and it is hard to completely understand all of its processes. The study of cold-blooded animals with large cells has thrown further light upon the matter, and in this way it has been possible to make a series of diagrams which make clearly evident what takes place in metakinesis.

According to Rabl, the closely wound mother-skein consists of several pieces, all of which turn at one end of the nucleus, the end that is called the polar field, leaving the pole itself free (Fig. 121, *a*). On the other hand, at the opposite end they pass across the pole (*b*). They run, therefore, at right angles to the long axis of the nucleus. The transition from the closer to the more open skein is brought about by the threads becoming thicker and shorter (Fig. 122). At the same time, some of them divide, so that the number of loops becomes greater.

The stage of the *segmented skein*, which follows next, is characterized, as Flemming has already stated, by *longitudinal fission of some of the loops*, so that the chromatic material is divided into two equal portions. The further course of karyokinesis is an effort toward the uniting of each of these halves of the chromatin threads into a new group.

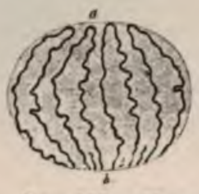

FIG. 121.—Close skein, viewed from the side.

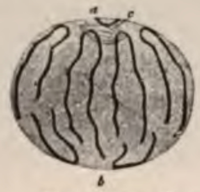

FIG. 122.—Open skein, viewed from the side.

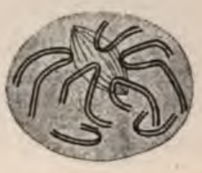

FIG. 123.—Final stage of the skein, with split threads.

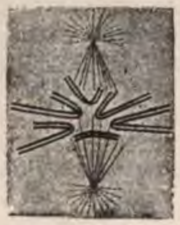

FIG. 124.—Mother-star.

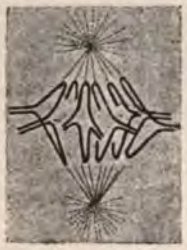

FIG. 125.—Metakinesis.

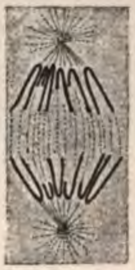

FIG. 126.—Daughter-stars.

During the stage of the coarse open skein a *spindle-shaped figure* has already come into view (Fig. 122, *c*), composed of delicate threads and terminating in small shining granules, the *centrosomes*. Later on, this spindle pushes deeper into the nuclear substance (Fig. 123) and exerts an influence upon the threads of chromatin. In the plane of its equator, later on, the division of the nucleus takes place.

To initiate the process of division the loops of threads group themselves about the equator of the spindle in such a way that the angle points toward the centre, the arms toward the periphery (Fig. 124). At the same time the nuclear membrane disappears, while radially arranged fibrils extend out from the poles of the spindle into the cell-protoplasm (attraction-spheres).

The stage characterized by the grouping of the longitudinally divided fibrils in the equator of the spindle corresponds to the figure designated *Mother-star* (Fig. 124). This, seen from above, looks like a star with a clear centre.

The *metakinesis* is characterized by a separation of the daughter-threads, which have resulted from the preliminary longitudinal division, and which up to this time had remained parallel with one another; and it is completed sometimes by a movement of part of the threads toward the opposite pole of the spindle (Fig. 125) (Heuser, Rabl). The new loops resulting in this way have their angles toward the pole.

The *daughter-stars* (Fig. 126) are formed by the chromatic loops that have moved toward the pole of the spindle, and whose limbs arrange themselves later on more nearly parallel to the equatorial plane of the spindle (Fig. 127, *a*).

The *daughter-cells* (*Dispirem* of Flemming), which proceed from the daughter-stars, consist of loops of fibrils which bend around at the point where the poles of the spindle are situated (Fig. 127, *a*) and leave a polar field (*c*, *d*) free from loops.

The transition from the skein to the lattice-work stage of the resting nucleus (Fig. 127, *b*) follows upon the division of the cell-protoplasm, and is initiated by the chromatic fibrils sending out processes. Flemming, Strasburger, Heuser, and Retzius believe that the chromatic fibrils are directly united one with another.

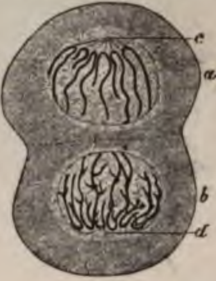

FIG. 127.—Daughter-skein, *a*, and daughter-framework, *b*; *c*, Polar area, with the remains of the spindle; *d*, Polar area.

The plan of division of the nucleus given by Rabl corresponds in the main with one already suggested by Flemming. Rabl believes that all nuclei possess a definite framework with thicker primary and more delicate secondary fibrils. At the commencement of karyokinesis the secondary fibrils are drawn in, while the primary fibrils, which have thus become distinctly visible, enter upon the changes above described.

According to Balbiani, Pfitzner, and Podwyssozki, Jr., the chromatic fibrils are composed of the finest granules, and it is probable (Flemming, Podwyssozki) that the granules are embedded in an *achromatic framework of threads* that do not stain.

The significance of the *nuclear granules* is still a matter of dispute. Flemming and Pfitzner believe that they are different from the nuclear framework, while others regard them as much-thickened nodal points of the framework fibrils. What becomes of them after division of the nucleus is not known.

The *elements of the nuclear framework* form at the periphery a denser basket-like layer, next to which on the outer side lies a membrane which does not stain.

Flemming and Hertwig believe that the *spindle-figure*, whose fibres are only imperfectly stained by nucleus-staining dyes, originates from the above-mentioned achromatic material of the nuclear framework, while Strasburger thinks that it comes from the cell-protoplasm.

The *centrosomes* or *polar corpuscles*, which always exist in nuclear segmentation, are present also in cells that are at rest. Nevertheless, up to the present time, they have been demonstrated only in a part of the cells, in largest numbers in lymph-corpuscles and in giant cells of the spinal cord. According to the investigations of von Kölliker, Flemming, M. Heidenhain, and others, it seems likely that the centrosomes belong to all cells, and lie sometimes in the protoplasm, sometimes in the interior of the nucleus, where they are difficult to demonstrate. This is because they do not stain with the ordinary nuclear dyes, but with acid aniline colors such as acid fuchsin and safranine. Whether they belong to the nucleus or to the protoplasm has not yet been made out. According to van Beneden, Beveri, and Rabl, the mitosis of the nuclear substances is to be explained on the ground of a direct drawing apart, starting from the divided centrosomes, and brought about by the agency of the achromatic fibres. According to Heidenhain, the central corpuscles are sharply circumscribed granules which possess the power of assimilation, of growth, and of multiplication by budding, by which means they are in the habit of forming groups. They may form the central point of insertion of a system of contractile fibrils (spindle-figure, microsome rays), whether alone or united into groups, and they consist of a specific substance in a chemical sense, which is not present in other parts of the cell.

§ 84. The division of the nucleus takes place in most cases in the way described in § 83, so that the nuclear figures shown on a preceding page become visible more or less perfectly. For the most part the figures are *bipolar*, although *multipolar mitoses* are not uncommon, in which three or more nuclei are formed at the same time. According to very recent investigations, **forms of cell-division also occur which differ more or less from the typical karyomitoses.**

In the first place, not infrequently mitoses take place which are remarkable for the unusual extent of the nucleus taking part in the division, and its *remarkable richness* in chromatin, which in these cases shows an irregular division into smaller and larger threads and masses. Then it often happens that the products of the division of the nucleus are unequal, so that *asymmetrical nuclear-division figures* result. This is observed especially often in carcinoma (Hansemann), but fairly often also in other new formations and in regenerated tissue-growths (Stroebe).

Moreover, not infrequently nuclei are observed which are remarkable for their peculiar and often very complicated forms; for instance, there are nuclei that have a ragged look (Fig. 128), from the fact that there extend out from the centre processes which have clubbed ends. Moreover, there occur rosette-shaped nuclei which form chains of oval or rounded elements, the chain being sometimes closed, sometimes open, or sometimes twisted. Then there may be basket-like figures (Fig. 129). Less striking, but nevertheless different from the normal, are the nuclear figures that have a knotted or ragged or bent or twisted appearance.

Such unusual nuclear forms are observed in the small and large cells (giant cells) of the spinal cord and spleen, as well as in the growths springing from bone (Figs. 128 and 129). In the same way the so-called multinuclear forms of leucocytes show ragged and festooned shapes in great variety, or nuclei composed of a number of parts united by bridges.

Fig. 128.

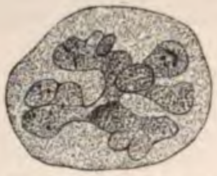

Fig. 129.

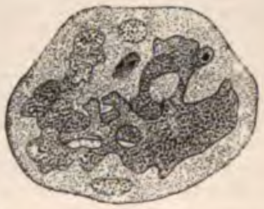

FIG. 128.—Giant cell with lobulated branching nucleus, from a sarcoma of the tibia. (From preparations by Nauwerck and Stroebe.)

FIG. 129.—Giant cell with basket-like nucleus, from a sarcoma of the tibia. (From preparations by Nauwerck and Stroebe.)

The exact significance of these nuclear forms is at present not known. In many cases it seems to be a matter of active or passive changes of form from movement of the nucleus or protoplasm, and which have nothing to do with the division of the nucleus (Arnold). In other cases these figures are observed in cells which are in process of degeneration, and this is especially the case with the leucocytes that have emigrated from the blood-vessels in acute inflammation. In still other cases this change of form leads up to division of the nucleus into several nuclei—a process that one has to regard not as a nucleus-destruction, but as the equivalent of a karyomitosis or as a true nuclear division, since the cells go on living (Arnold) and under some circumstances may even undergo division. In favor of this interpretation, also, is the fact that in these cases an increase in the chromatin is observed, by means of which it forms threads or masses or is more diffusely distributed.

Yet it is to be noted that there are no observations which prove that through such processes of nuclear division newly produced cells are capable of forming new tissue.

If the pinching off of nuclei from such a nuclear mass is associated with an increase in the chromatin, then Arnold names this process *indirect fragmentation;* or if such an increase does not occur, *direct fragmentation.* The pinching off of nuclei is ushered in by a heaping up of the chromatin in those areas that are to become nuclei.

By the observations of Flemming, Arnold, Denys, Nauwerck, and others, it has been proved that also a division of the nucleus takes place through a constricting off, as was formerly assumed to be general and typical—a form of division which Flemming calls *holoschisis.* Arnold calls it *direct segmentation,* while he applies the term *indirect segmentation* to the mitotic division by which a multiplication and typical rearrangement of the chromatin takes place. Lately all the forms of nuclear division which do not take place by mitosis have been included under the term **amitotic nuclear division.**

Arnold, as the result of searching histological and experimental investigations on normal and pathological tissues, recognizes four types of division of the nucleus. *Segmentation* he names a division of the nucleus in the equatorial plane, or segmental plane, into two or more approximately equal parts. He distinguishes a *direct segmentation,* in which the division takes place without increase or altered arrangement of the chromatic nuclear substance, and an *indirect segmentation,* in which the chromatic division-figures already described occur. *Fragmentation* he calls a pinching off of the nucleus at some point into two or more equal or unequal portions, which are not limited by smooth division-surfaces. In this case, too, he distinguishes an *indirect form* with increase and altered arrangement of the chromatic nuclear substance, and a *direct form* taking place without these. In indirect fragmentation the arrangement of the threads according to definite rules is lacking, and the pinching off of the nuclei and cells is accomplished irregularly. His investigations were made upon the cells of the spinal cord, the lymph-glands and spleen, and upon the multinuclear cells from tumors and inflamed lymph-glands, as well as upon wandering cells and giant cells, which in frogs migrate into foreign bodies.

According to Arnold, there are no considerable differences between segmentation and fragmentation, it being rather a matter of slight variation. In fragmentation there is wanting the typical arrangement of the chromatic fibres in the stage of equatorial transposition. At the same time the outlines of the nuclear membrane remain sharply defined, while in indirect segmentation they are lost. According to Arnold, atypical forms of nuclear figures occur especially often in the spleen of white mice.

It is probable that all the forms of amitotic or direct division occur only in cells which no longer possess any tissue-forming activity. In favor of this view is the fact that they take place especially in those cells (leucocytes) which are in process of retrogression, and that they are absent in physiological tissue-formations as well as in tissue-growths in process of regeneration and hypertrophy. According to Flemming's observations, division of the attraction-spheres and the central corpuscles does not take place in the amitotic division of leucocytes. According to H. E. Ziegler, the nuclei which suffer amitotic division are for the most part distinguished by their extraordinary size, and are especially those nuclei which are associated with an intense process of assimilation or secretion. Löwit, on the contrary, holds that amitotic division, as he has observed it in leucocytes, is in part the equivalent of mitosis, but in some cases is followed by cell-degeneration.

§ 85. The changes in the structure of the nucleus are a clear indication of the marked activity which is going on in the elemental parts of the nucleus in productive processes. Unfortunately our knowledge of the **changes in the elements of protoplasm** is scanty and incomplete; yet it can be demonstrated that protoplasm also possesses a special structure of its own, and that here also various transpositions of the separate parts in relation to one another take place; for instance, in some cases, during the division of the nucleus, active rotary movement of the protoplasm has been observed. As a result of such movement and change of position of the separate parts may be mentioned the formation of the above-mentioned clear area about the dividing nucleus, as well as the formation of ray-like granular fibres at the poles of the nuclear spindle. Lately, indeed, there has been a tendency to ascribe to the centrosomes situated in the interior of the radial figure an important rôle in the division of the nucleus, and to recognize in them, or in the nucleus, preëxisting centres (van Beneden, Boveri), whose division gives rise to the division of the nucleus.

Between nucleus and cell-protoplasm there exists probably a very complicated relationship. Yet **the nucleus is to be regarded as the more highly organized material,** as **the centre of power for the cell.** *It is through the nucleus that the characteristics of the cells are transmitted to their descendants* (Hertwig, Kōlliker, and Weismann), *while the protoplasm governs their relations with the outside world* (Haeckel), attends to nutrition, and takes part in tissue-formation. It is, however, to be noted that the metabolic phenomena also, which go on in the interior of the cells, as well as the motor function of the cells, are under the influence of the nucleus.

The radial arrangement of the protoplasm granules, as well as their movements which have been studied up to the present time, takes place for the most part simultaneously with the process of nucleus-division. In other cases they follow it. In still others they precede it. Thus, for example, according to Gruber, *Euglypha alveolata*, a rhizopod, forms first a daughter-cell, with all its attributes; then the nucleus enters upon the stage of division and migrates into the daughter-cell. At the same time active movements are set up in the protoplasm.

The **division of the cell-protoplasm,** as a rule, follows close upon division of the nucleus, and takes place, ordinarily, in the stage of the daughter-skein; yet the relation of the two processes to each other is not such that the latter must necessarily occur. Not infrequently, in spite of division of the nucleus, cell-division does not take place. The result of this is the formation of cells with two or more nuclei, the so-called **giant cells.** By multipolar mitosis, or nuclear fragmentation, multinuclear cells may proceed from uninuclear. In the latter case one finds as forerunners of the multinuclear cells giant cells with complex nuclear figures (Figs. 128 and 129). These giant cells may, later on, break up into uninuclear cells, by the concentration of the protoplasm around the various nuclei, and the development of lines of demarcation between their different areas. Yet it must be noted that the giant cells that result from amitotic division, as far as is known, do not break up into separate cells. In the division of giant cells whose nuclei have multiplied by mitosis, it may happen that the cell separating itself off from the rest may still be completely surrounded by the protoplasm of the parent-cell. Virchow has called these brood-cells. They are not often met with. They were regarded as more common than they really are, because round cells that had been taken up by larger cells were regarded as a young brood of cells (see Catarrhal Inflammation of the Mucous Membranes).

The process of cell-division presents a peculiar appearance in the **formation of offshoots and buds,** the parent-cell throwing out a shorter or longer process which contains nuclei and later on separates off from its parent-cell (cf. Formation of New Vessels). The peculiarity consists in this chiefly: that independent movements are set up in the protoplasm with the formation of processes, and that the nuclei which multiply by division of the parent-nucleus only subsequently migrate into the process.

Flemming defines a cell as a circumscribed mass of living matter, and distinguishes in a *cell-body* two separate elements, of which one, the protoplasm (*mitom, framework*), is somewhat more strongly refracting and is arranged as a network, while the other, the paraplasm (*paramitom*), fills the remaining space. The minuter structure of the protoplasm cannot be made out. Products of metabolism—granules, vacuoles, and other matters which the cells sometimes contain—do not belong to the cell-substance itself.

§ 86. The **formation of new cells by the division of preexisting ones** is the first step in hyperplasia, as well as in regeneration. This results in the **formative tissue,** from which the specific tissue will be developed.

Just as the process of nucleus- and cell-division in the development of pathological formations is closely allied to that of normal cell-proliferation, so also are the further developmental processes throughout similar to the normal. If epithelial tissue or any form of connective tissue is to be formed from the material produced by cell-division, then the same transformations occur as in normal growth.

As far as present investigations go, the law of the **specific character of the tissues** holds good. The offspring of the various germinal layers which are differentiated in the earlier embryonic period are capable of producing only those tissues which belong to their special layers. An epithelial cell cannot produce cartilage or bone or connective tissue; and a connective-tissue cell is unable to give rise to epithelial or gland cells. This law has often been questioned—that is to say, such a specific character was not ascribed to the tissues. Virchow, whom we have to thank for the first investigations into the cellular processes in pathological new growths, believed that the connective tissue is the matrix for the most widely different tissues. Such a view we are no longer able to hold. On the contrary, observation proves that each tissue is capable of producing only tissues like itself or closely related to it.

The formation of epithelial tissue is brought about by the uniting together of the respective cells by means of cement substance in the manner characteristic of this tissue. In the case of connective tissue, the formation of the intermediate substance from the cells becomes a more prominent feature, and its nature gives to the tissue itself its characteristic properties.

The fertilized ovum is capable of forming, by its progeny, all the various tissues of the body, and we have to assume that this capability is situated in the nucleus, which is the seat of the inherited characteristics. With the advancing differentiation of the tissues there comes a simplification of the structure of the nucleus; that is, a special protoplasmic impulse obtains control, so that now the cell is capable of producing only a special kind of tissue. The statements therefore are in error which say that from epithelium connective tissue may be formed, or from connective-tissue cells, gland-tissue, or nerves. According to

Hansemann, the specific quality of the cells is indicated not only by the special structure of the complete cell, but also by the course of the karyokinesis, since individual differences in this process occur in the different kinds of tissue, by which one can recognize the separate tissues by the form of their mitosis (size, number, and shape of the chromosomes).

Most recently, Grawitz * has advanced the view that *cells may also arise from intercellular substance*, and he claims that, in the formation of connective tissue, cells are transformed into fibres, and pass over into a *resting stage*, in which nuclei are no longer visible under the microscope. From these invisible *resting cells* (*Schlummerzellen*) new cells are formed again in inflammation and tissue-growth. By means of this rest theory, Grawitz has brought again into discussion, as a new teaching, views which years before Stricker and Heitzmann had offered; but the work done by himself and his pupils in his institute contains nothing which substantiates his view. The well-known phenomena of growing and inflamed tissue are described, and there are no observations communicated which can be regarded as proving that cells may spring from intercellular substance—that is, from invisible resting cells

§ 87. Any new formation of tissue, then, is conceivable only if the preëxisting cells also possess the power of multiplying. This power, according to our experience, belongs to most of the cells of the human body; yet we do know cells, also, which have lost this power, and these are cells that suffer a marked transformation in the development of the tissues. For example, the cells of the horny layer of the epidermis and the non-nucleated red blood-cells are no longer capable of producing new cells. Very probably, in fully grown individuals, this power is lacking in the ganglion-cells and bone-cells. Pavement epithelium, gland-cells, connective-tissue cells, periosteum- and marrow-cells possess, on the contrary, a very marked power of regeneration, and may in certain cases develop an excessive growth.

Most of the body-cells have the **power to proliferate,** and many forms of tissue are able to go on growing for a certain length of time when separated from the parent-soil. The possibility of **tissue-transplantation** depends upon this property—that is to say, the possibility of transplanting portions of tissue from one locality to another, and having them go on growing.

Attempts at transplantation are very old, and have been made upon various tissues; for instance, periosteum and marrow have been transplanted to soft parts or into blood-vessels, and made to grow there (Ollier, Goujon, Bruns, Barkow, Philippeaux, Cohnheim, Maas, and others). Further, the spurs of young cocks have been transplanted to the combs of other cocks, and rats' tails have been successfully brought under the skin of the back of other rats (Duhamel, Hunter, P. Bert). Some years ago Hanau succeeded in transplanting cancer tissue from one animal to another.

The most numerous transplantations of tissue have been made with skin. The investigations of Reverdin and Thiersch gave the impulse to the utilization therapeutically of *skin-transplantation* for the healing over of broad, open wounds. The same procedure is made use of when completely separated pieces of skin are to be made to heal over at the point of separation.

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* Grawitz, "Ueber die schlummernden Zellen des Bindegewe
Verhalten bei progressiven Ernährungstörungen," *Virchow's*
1892; "Atlas der pathologischen Gewebelehre," Berlin, 189

For successful transplantation—that is, transplantation followed by multiplication of the cells and formation of new tissue—only those structures are suitable whose cells are capable of rapid growth—for example, epithelium and periosteum. Bone and cartilage of adult animals, for example, do not go on to growth if transplanted, while embryonic cartilage does grow (Leopold and Zahn). It seems also to be a matter of importance that the tissue transplanted should have a certain amount of firmness and coherence. This, at least, is indicated by the fact that after the burying of living embryos in the tissues or in the abdominal cavity of an animal, only the firmer tissues—as, for example, cartilage—last a considerable time and show evidences of growth. Finally, it is to be noted that growth takes place only if the tissue is transplanted on to an individual of the same species.

Furthermore, it is noticed that *the growth of the transplanted portion is usually very limited*, especially of pieces that are sunk deeply into the body, so that this growth, after a time, comes to a standstill, and even *goes on then to resorption, thus bringing about the disappearance of the transplanted piece*. In general, only skin-grafting produces lasting tissue, and even in this case part of the tissue is absorbed.

Skin-grafting can be undertaken as well in fresh as in granulating wounds—that is, wounds where the tissues infiltrated and inflamed are in a state of active growth. In these cases, one cuts with a sharp knife thin strips of skin which contain not only the epithelium, but also the tips of the papillæ, and in part also the uppermost layers of the corium. These are laid upon the fresh wound—that is, upon the subcutaneous tissue, fascia, muscle, periosteum—or upon the shaved-off granulations, and pressed firmly in place by moistened gauze. The fastening of the strip upon the wound-surface takes place by coagulated lymph or coagulated blood. In successful cases, in eight days they are firmly united.

The nourishment of the transplanted pieces takes place, first, by the taking up of material from the exuded tissue-fluids. Later on, there rises up from the subjacent surfaces embryonic tissue, with vessels, which makes its way through the superjacent coagulum into the transplanted structure, so that its connective tissue contains new vessels. The upper horny layers of the epithelium are desquamated. The deeper layers begin to grow from the second day on, and form new epithelium, on the surface of which, later on, a horny layer appears. If connective tissue is transplanted with the epithelium, then its cells may also go on to grow and produce connective tissue. According to the observations of Goldmann, however, the elastic fibres which are to be seen later in the grafted portion come from the surrounding tissue. Later on—that is to say, after the lapse of several weeks—there not infrequently occurs a shedding of the epidermis. Nevertheless, when the transplanted skin has once healed and begun to grow, it is generally permanent.

§ 88. If the cells of a tissue enter upon a process of division which exceeds what is customary and what may be regarded as normal, so that in this way a hypertrophic development of the tissue in question results, **the cause of this pathological growth** may be the fact that the cells go on to an excessive multiplication by reason of a special **inherited disposition** on the part of the tissue. This inherited tendency may consist in either abnormally vigorous vital impulse, an abnormal property of the nuclear material, an abnormal number of the embryonic cells belonging to the tissue, or a lessening of the inhibitory influence of the environment or of the organs having a special relation to the portion of tissue in question. If from the course of the hypertrophic growth the existence of a congenital cause can be excluded, then the first of the above possibilities may be disregarded, and we can explain the pathological growth only on the ground of a lessening of the obstacles to growth, or an increase of the forces stimulating development. The same holds good also for all new formations having the character of regeneration.

Of the authors who have expressed opinions regarding the causes of pathological new growths, some have regarded as the essential cause of the onset of the cell-division a lessening of the obstacles to growth; others have explained it on the ground of an increase in cell-activity. Virchow took the position that the cell is a body which has a certain *susceptibility to stimuli—an irritability;* that by certain influences—by irritants—it can be stimulated to an increase in its activity, and, indeed, as well in the sense of an increased functional activity as also in that of an exaggerated nutrition, division, and multiplication; and he spoke accordingly, also, of *functional nutritive and formative irritability of the cells.* If one accepts this view, then the solution of the above question is to be found in the *explanation of those stimuli which urge the cells to growth, as well as of the obstacles which check the cells in the exercise of their power of proliferation.*

As far as **inhibitory influences capable of restricting tissue-growth are concerned,** these seem to exist, from the fact that many cells, although they are capable of division, yet do not go on to multiplication, and seem to be inhibited in their division. This inhibition may depend upon their general relation to their environment and its mechanical influence, as well as upon chemical influences or upon some specific effect of their surroundings (Roux). The firm embedding of the cells in the tissues, together with the observation that, after breaking up and absorption of the intercellular substance, cell-proliferation takes place, speaks in favor of the view that in the actual growth of the tissues an inhibitory influence is developed toward further division of the cells. How much influence, also, the chemical composition of the fluid about the cells has is hard to determine. If one considers the conditions as they exist at the onset of regenerative growth, one gets the impression that, in the first place, a lessening of the inhibition of growth is associated with the breaking up of the union of the elements, or with their separation, although this does not exclude the possibility that changes in the chemical nature of the tissue-fluids may work in the same way. Furthermore, it is also possible (Roux) that the specific influence of environment may be abolished by the destruction of specifically differentiated cells, and that in this way the mechanism of regeneration is aroused in neighboring, and later on also in more distant cells.

Among the **influences that are capable of increasing the power of proliferation of a cell,** the supply of nourishment has often been given a prominent place, and accordingly it has been thought that new growths may be explained on the ground of frequently recurring or persistent hyperæmia. Against this view, however, it must be remarked that there is no real proof of its correctness; that congestive hyperæmia and increased nutritive supply may render possible an increase in the process of nutrition, in that the cells may, under these circumstances, take up more nourishment, on account of increased flow of blood to the part; but there is no proof that this actually does take place. The essential fact is, not that the cells are nourished, but that they nourish themselves. If an increase in the nutritive processes is to take place, the cell itself must be stimulated to bring it about.

The stimulus which impels a cell to such an increase is often an *increase in its own activity.* Much hypertrophy is hypertrophy from activity, and if in these cases cell-growth takes place, it is brought about by the same influences that caused the increased activity in the first place. In the case of muscle, it is an increase in the nerve-stimulus. In the case of the kidneys and the liver, the stimulus to activity, and consequently, also, the cause of hypertrophy, are to be found in chemical changes in the composition of the blood which is conveyed to these organs for the secretion of specific substances.

How far, in the case of the rest of the tissues, changes of innervation or changes in the composition of the blood and tissue-juices can stimulate the cells to an increase in their formative activity is at present hard to determine. Formerly it was generally believed that by various mechanical and chemical influences or irritants cell-growth could be brought about; but exact investigations have indicated that by such procedures first a tissue-lesion is produced—that is to say, cell-degeneration and cell-necrosis—and that the growth follows upon this as a secondary matter. Moreover, more recent observations make it seem probable that there are chemical substances which can act upon cells as stimuli to growth. Should this prove to be correct, it would follow from it that not only in the case of gland-cells, but also with other cells, *cell-proliferation takes place sometimes from removal of obstacles to growth, sometimes from the operation of formative stimuli* which are of a chemical nature, or, in the case of muscle, through nerve-influence, or *sometimes from a combination of these two.* The formative stimuli may be either those always present in the organism, physiological, but becoming excessive under pathological conditions, or they may be the result of chemical substances from without.

The views of different authors upon the causes of tissue-growth are very different. This is the result of the fact that these phenomena elude accurate investigation, and so we must turn to hypotheses. In the present article it is impossible to enter upon a discussion of the different views. I have collected them in my work upon the causes of tissue-growth,* and have there more accurately defined my own views. That over-nourishment is by itself incapable of bringing about a new growth is to a certain extent evident, since in animals an increase of flesh cannot be brought about, but only an increase of fat. According to Penzo, in young animals a growth of tissue is markedly encouraged by a temperature of from 37° to 40° C. (98.6° to 104° F.). By a temperature of from 10° to 12° C. (50° to 53.6° F.) growth and cell-regeneration are lessened. Roemer believes that the introduction into the blood of a fluid containing protein causes an increase of the leucocytes by division.

II. The Processes of Hyperplasia and Regeneration in the Various Tissues.

§ 89. The morphological changes in the **regeneration and hyperplasia of epithelium** are comparatively simple. The karyomitoses (Fig. 130, *a–d*) correspond in the main to those described in § 83. The division of the protoplasm ensues either in the later stages of the process of nucleus-division or follows after it. Sometimes processes are formed first from the proliferating epithelium, into which, later, nuclei migrate. These processes become independent by separation from the mother-cell.

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* Ziegler, "Ueber die Ursachen der pathologischen Gewebsneubildungen," *Internat. Beiträge, Festschrift für Virchow*, Berlin, 1891.

Epithelium springs only from epithelium, and, moreover, the various forms of epithelium do not pass over into one another. It is, however, to be noted that under certain conditions—for example, in cases of inflammatory irritation of long standing—epithelium which is regenerating may change its character; so that pavement epithelium may be developed on surfaces which originally possessed ciliated cylindrical epithelium. This may happen, for example, in the case of cicatrices in the bronchi. Lesions of ciliated epithelium are in the first place repaired by flat cells, which later on are transformed into high or cylindrical cells.

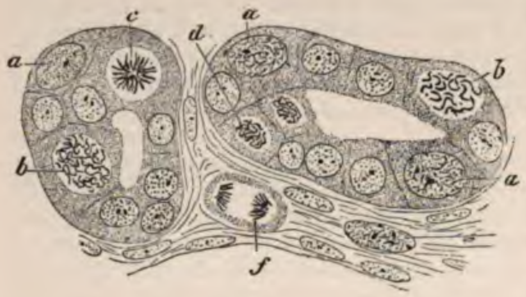

FIG. 130.—Regeneration of the epithelium of the biliary passages in the neighborhood of a wound five days old. *a*, Enlarged nucleus of epithelial cell, with increased chromatin; *b*, Epithelial cell with mother-skein; *c*, Epithelial cell with mother-star; *d*, Epithelial cell with daughter-skein; *f*, Connective-tissue cell with daughter-star. (Preparation hardened in Flemming's acid-mixture, and stained with safranine and picric acid. Magnified 400 diameters.)

Slight losses of substance in the superficial epithelium are generally quickly replaced by regenerated growth in the neighborhood. In the intestine a lesion of the epithelium is very rapidly healed by a growth of the epithelial cells situated in the deep parts of Lieberkühn's follicles. In the same way, glandular epithelium—for example, in the kidneys—is quickly replaced after loss, provided the structure of the tissue—that is to say, the substratum upon which it rests—is not changed or destroyed. After destruction of liver-tissue the liver-cells, as well as the epithelium of the bile-ducts (Fig. 130), are developed, and when the liver is injured the division of the nuclei of the liver-cells may occur at a comparatively great distance from the wound. Artificial defects and incisions in gland-tissue are closed over by new-formed connective tissue, into which, however, more or less extensive new-formed glands grow. Gland-ducts may put out offshoots in regenerated and hypertrophic growths in the same way as in embryonic life. In the intestine, if from an ulcerative process a part of the mucosa and submucosa is lost, in the course of healing a gland-development takes place which, according to the nature of the defect, produces sometimes typical, sometimes rather atypical new glands (Fig. 131), which grow down into the submucosa. The new gland-formation proceeds from the old glands, whose epithelium pushes forward over the edge and the base of the ulcer (Fig. 130) and lines the crypts (*k*). In the same way, also, in the stomach, erosions are healed over, and ulcers even of considerable extent can be covered with mucous membrane containing glands, though, to be sure, the glands do not generally possess a typical form.

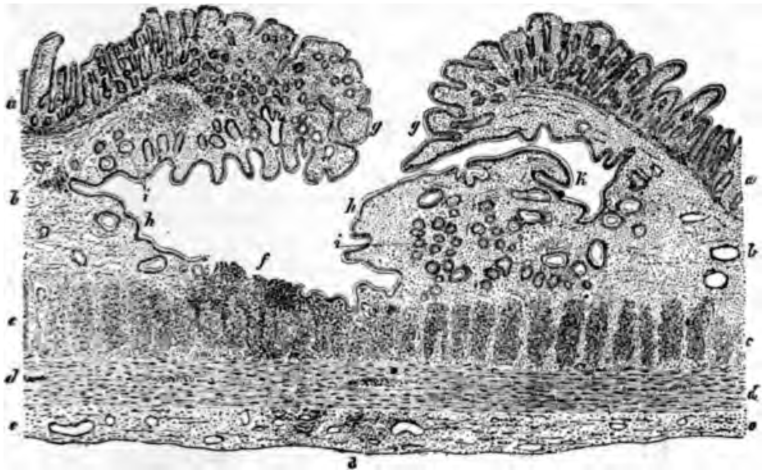

FIG. 131.—Healing of an ulcer of the small intestine, with formation of new gland-tubes in the submucosa. *a*, Mucosa; *b*, Submucosa; *c*, *d*, Muscularis; *e*, Serosa; *f*, Rest of the base of ulcer not yet covered with epithelium; *g*, Overhanging edge of ulcer; *h*, Base of ulcer covered with epithelium; *i*, New-formed glands situated in the submucosa; *k*, Deep crypt covered with epithelium. (Preparation hardened in Müller's fluid, alcohol, and celloidin; stained with hæmatoxylin; mounted in Canada balsam. Magnified 20 diameters.)

If **compensative hypertrophy** takes place in a kidney or liver, as a consequence of loss of kidney- or liver-tissue, it is brought about by the formation of new gland-cells and enlargement of existing gland-tubes and stroma. After extirpation of a kidney the commencement of compensatory hypertrophy may, under some circumstances, occur on the third day with the appearance of nuclear-division figures in the epithelium of the urinary canals, and then there takes place a further permanent growth of the epithelium of the tubules and the glomeruli, as well as of the cells of the vessel-walls.

The regeneration of epithelium has been the subject of many investigations in recent years, but an insight into it has been rendered possible only by a knowledge of the nuclear-division figures. In the first place the regeneration of superficial epithelium was studied. Lately gland-regeneration also has been investigated, and in this connection reference must be made especially to the work of Bizzozero, Vassale, Griffini, Poggi, Podwyssozki, Coën, and Obolonsky. The work of the three last named was carried out in my institute, where, for a number of years, systematic investigations upon tissue-regeneration have been made.

§ 90. The **new formation of blood-vessels** plays an important part in the hyperplasia of the most varied tissues. If connective tissue, bone, or gland is to be reproduced in any considerable amount, the new formation of blood-vessels is essential, since only by means of these can sufficient nutriment be brought to the growing tissue; consequently the vessel-formation appears very early in tissue-growth, and is to be regarded as by all means the most important factor in its development.

The development of new blood-vessels takes place by the **formation of offshoots** from the wall of preëxisting vessels (Fig. 132). Shortly after, or at the same time with, the formation of the offshoot, or even earlier, a **growth of the cells of the vessel-wall** takes place—that is, of the **endothelium** (Fig. 133)—in which nuclear division occurs by **karyomitosis.**

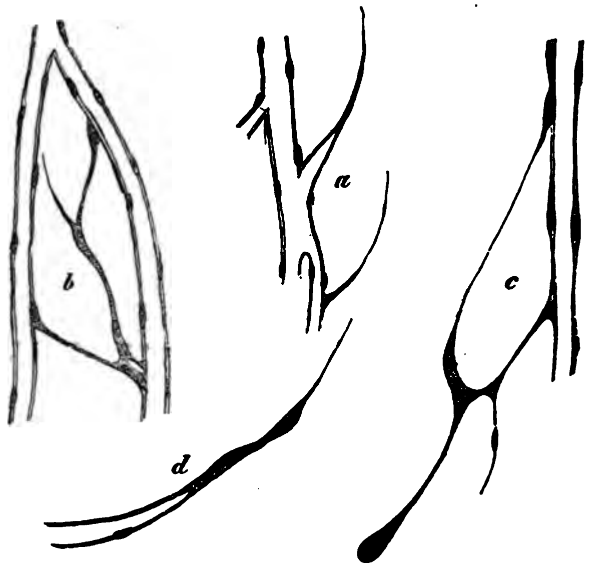

FIG. 132.—Development of a blood-vessel by formation of offshoots, from preparations which were taken from a formation of inflammatory granulations. *a, b, c, d,* Different forms of offshoots—some solid (*b, c*), some becoming hollow (*a, b, d*), some simple (*a, d*), some branching (*b, c*), some without nuclei (*a, d*), some with nuclei (*b, c*). Formative cells have applied themselves to the outside of the offshoots.

As the first indication of a new vessel, one notices on the outer side of some capillary loop a tent-shaped elevation, which terminates in a fine protoplasmic thread, standing out from the vessel, and which becomes longer and longer, while at the same time, also, the granular mass grows. In this way there is then formed a *solid granular arch of protoplasm*, which ends in a *thread of protoplasm*, and after a certain time contains nuclei. It may penetrate into another vessel or unite with some other arch which it meets, or finally return again to the same vessel from which it started.

Furthermore, from the arch itself new arches may spring (Fig. 132, *b, c*), or it may end in a club-shaped process.

The arch, which in the first place was solid, after a certain time becomes hollow (*b, a*) by the liquefaction of its central part, and this space either at once or very soon comes to communicate with the lumen of the blood-vessel (*a*), or else there is developed a protrusion of the lumen of the vessel at the seat of the arch. The blood of the parent-vessel makes its way at once into the cavity of the daughter-vessel and widens it out. By reason of the fact that the hollowing out advances and extends to the point of entry of the protoplasm-arch into another blood-vessel, there is formed a new capillary loop permeable for blood.

The arch of protoplasm which raises itself from the wall of a blood-vessel is to be regarded as a process of a cell of the vessel-wall, and later on, after it has acquired a nucleus, it comes to be an independent cell. Accordingly, *the blood-vessels arise from the hollowing out of a filiform cell.*

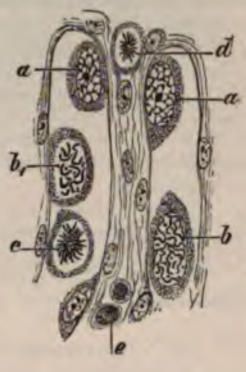

FIG. 133.—Two vessels of the papillary layer, whose endothelial cells are in process of growth; five days after painting the skin of the back of the foot with iodine. *a*, Nucleus with chromatin framework; b, b_1, Skein forms; *c*, Mother-star; *d*, Connective-tissue cell with nuclear division-figure; *e*, Uninuclear leucocytes. (Preparation hardened in Flemming's acid-solution and stained with safranine and picric acid. Magnified 350 diameters.)

Immediately after the opening of the way for blood, the capillary is a tube with a homogeneous wall. After a certain length of time the protoplasm gathers itself about the nuclei, which have in the meantime divided and multiplied so that eventually the capillary is made up of pavement epithelium. As Arnold has shown, the line of division between the separate flat cells may be demonstrated by injecting a solution of silver into the vessel (endothelial cells). At this time the wall appears already materially thickened, partly from growth of the cells themselves of the vessel-walls, but partly also because a considerable number of the formative cells of the neighborhood heap themselves upon the surface of the young vessel (Fig. 132, *d*), apply themselves to the wall, and so make it thicker.

The process of new vessel-formation consists mainly of the phases of development. It seems, however, that a new feature may appear in the process of development, in that spindle-shaped or club-shaped or branched formative cells may become associated with the processes of the vessel-walls, and then, in the same way as in the case of the protoplasmic arches, be transformed into capillaries, by the development of a central canal.

At the time of the formation of the offshoots, the endothelial cells of the capillaries are much swollen, and sometimes in growing tissues they reach such a size that the cross-section of a capillary looks not unlike a gland-duct lined with epithelium (Fig. 134, *d*).

At the same time, nuclear-division figures appear in the endothelium (Fig. 133, *a–c*), which later on are followed by division of the nucleus and cell. In just what relation these growths stand to the bud-formation has not yet been clearly made out, but doubtless the buds spring from growing cells. The growth of the endothelium, however, does not always lead to the formation of new vessels, but may only bring about a thickening of the wall, and finally an obliteration of the lumen.

If the new-formed capillaries are to become arteries and veins—a change which in the case of extensive new growths must always occur in a part of the capillaries—this takes place by a growth of the cells of the vessel-wall. The different parts of the arteries and veins are developed om this formative material by special processes of differentiation.

In the handbooks of pathological anatomy and surgery, three forms of new formation of vessels are generally described, and distinguished as primary, secondary, and tertiary.

In the primary form the cells of the germ-tissue are directly transformed into red blood-cells and the elements of the vessel-walls, and this takes place as follows: the germ-cells unite together to form strings, whose axial portions become red blood-cells, while the peripheral parts become the structure of the wall. This form of vessel-development, which occurs in the embryo, does not take place pathologically.

In the secondary germ, according to Billroth, O. Weber, and Rindfleisch, spindle-cells unite to form cords in such a way that they inclose between them a canal.

As far as I can see, these observations are based upon errors; because, very early, spindle-cells heap themselves upon the vessel-buds—for example, in granulations—cover over the buds, and form strings of cells about them.

The so-called tertiary formation is that which has been described in the main text.

§ 91. The **connective-tissue structures** are almost all capable not only of a hyperplastic, but also of a regenerative growth. This especially holds good of unformed and formed connective tissue, the periosteum, marrow, and lymphadenoid tissue, while cartilage possesses only a feeble power of regeneration, and the completely developed bone takes no share in the new formation of bone-tissue. In case of destruction of connective tissue the substitution tissue newly formed by regenerative growth is very often not the same as the original tissue. More often another form of connective tissue comes in its place. Thus defects in cartilage are for the most part replaced by connective tissue or by bone, and in the place of destroyed fat, lymph-glands, tendons, etc., there is developed thick, fibrillated connective tissue—so-called *scar-tissue*.

Hyperplastic and regenerative growth of connective tissues is ushered in by *cell-multiplication*, in the course of which the above-described karyomitoses occur (Fig. 130, *f*; Fig. 133, *d*; Fig. 134, *b*, *c*).

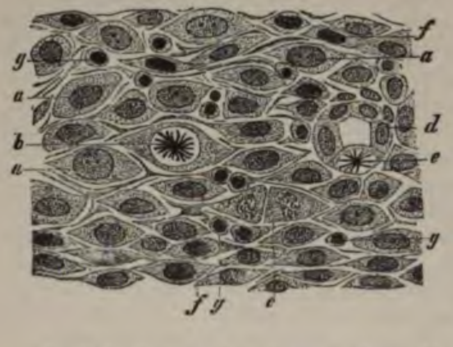

FIG. 134.—Proliferating periosteum, four days after fracture of a bone. *a*, Pale formative cells with large nuclei; *b*, Osteoblast with nuclear-division figures; *c*, Two cells soon after division, showing thread-skein in nucleus; *d*, Blood-vessel with proliferating endothelium; *e*, Endothelial cell with nuclear figure; *f*, Small dark-colored formative cells; *g*, Leucocytes. (Preparation treated with Flemming's nucleus-fixation fluid and hæmatoxylin, and mounted in glycerin. Magnified 25 diameters.)

In injuries to the tissues, the cell-proliferation begins very early, so that, for example, in fractures of bones, already on the second day single cells of the periosteum have enlarged and show nuclear-division figures. In regeneration and hyperplasia after slight injuries, here and there karyokinetic figures occur, and lead soon to the formation of new cells (Fig. 133, *d*).

If only a few cells are destroyed by an injury to a tissue, new-formed cells are developed in the place of those lost, without any considerable change in the structure of the tissue taking place. If, on the contrary, under pathological conditions, a considerable amount of new structure is formed in a short time, the proliferating cells form an **embryonic tissue** consisting for the most part of cells and blood-vessels (Fig. 134). The extent of this, naturally, may vary considerably, and depends partly upon the capacity of the tissue for proliferation, partly upon the nature of the lesion which leads to the proliferation. For example, the periosteum, proliferating after fracture of a bone, forms a continuous layer of developing embryonic tissue (Fig. 134), while proliferating cartilage generally produces only small foci consisting of a limited number of cells.

The proliferating cells are always larger than those of fully developed and quiescent connective tissue, and contain large bladder-shaped nuclei with nucleoli. They have for the most part one or two nuclei (Figs. 134 and 135), though multinuclear cells also occur (Fig. 135, c_1)—the so-called *giant cells.*

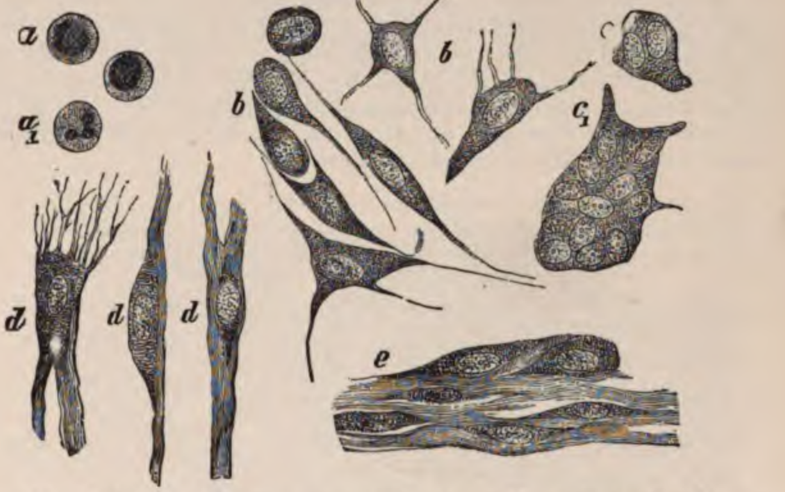

FIG. 135.—Isolated cells from a granulating wound. *a*, Uninuclear leucocyte; a_1, Multinuclear leucocyte; *b*, Different shapes of uninuclear formative cells; *c*, Double-nucleated formative cells; c_1, Multinucleated formative cells; *d*, Formative cells in the process of tissue-formation; *e*, Completed connective tissue. (Picrocarmine preparation. Magnified 500 diameters.)

Since all of these cells are the antecedents of the future tissues, they are called **formative cells.** If connective tissue is to develop later from the embryonic tissue, then these cells are called **fibroblasts** (Fig. 135, *b, c, d, e*, and Fig. 136, *a*). The antecedents of cartilage and bone are called **chondroblasts** (Fig. 137, *a, c*) and **osteoblasts** (Fig. 134, *a, b, c*).

The shape of the formative cells may vary (Fig. 135, *b, c, d, e*), and depends in part upon internal causes—that is, upon changes in shape spontaneously developed—in part upon the influence of the environment, which under certain circumstances compels the cells to take certain definite shapes. The most varied shapes occur in the cells which produce connective tissue.

If **connective tissue** is to be developed from an embryonic tissue, either fine *fibrillæ* (Fig. 135, *d*, *e*) appear at once in certain parts of the cell-protoplasm and between the cells, or else there appears first a *homogeneous intercellular substance* (Fig. 136, *b*), in which, subsequently, the fibrillæ become differentiated. The formative cells meanwhile diminish in size, and come to lie in small clefts (Fig. 135, *e*) which are situated in the basement substance.

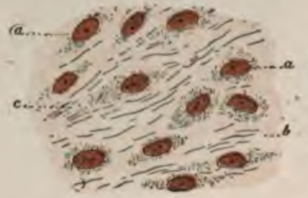

FIG. 136.—Development of connective tissue from fibroblasts. *a*, Fibroblasts; *b*, Hyaline basement substance with separated fibrils; *c*, Fibrils around fibroblasts. (Preparation hardened in Müller's fluid, stained with picrocarmine, and mounted in glycerin. Magnified 400 diameters.)

In the development of **hyaline cartilage** there appears between the cells a hyaline basement substance (Fig. 137, *f*), while the chondroblasts (*c*) at the same time take on a more rounded form (*d*). As time goes on the basement substance increases, and the chondroblasts grow smaller, and come to lie in rounded cavities whose walls are denser than the rest of the basement substance, and later on form the part of the ground-substance which is called cartilage-capsule.

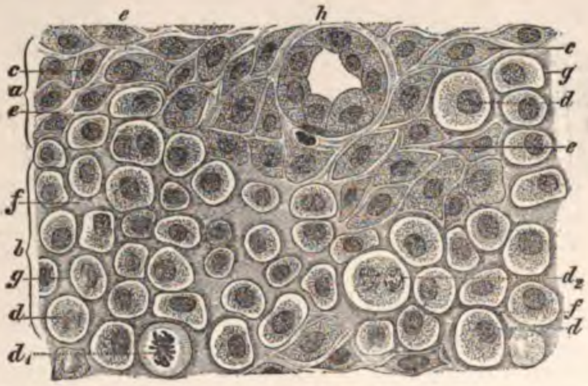

FIG. 137.—Periosteal cartilage-formation in a fracture five days old. *a*, Cellular embryonic tissue; *b*, Cartilage-tissue; *c*, Proliferating periosteal formative cells; *d*, Cartilage-cells; d_1, d_2, Nuclear-division figures in cartilage-cells; *e*, Basement substance of the embryonic tissue; *f*, Basement substance of the cartilage; *g*, Cartilage-cell capsules; *h*, Proliferated endothelium of a blood-vessel. (Preparation treated with Flemming's nucleus-fixation fluid and hæmatoxylin, and mounted in glycerin. Magnified 250 diameters.)

If **bone** is to develop from cellular embryonic tissue there appears between the formative cells a homogeneous or fibrillated dense basement substance (Fig. 138, *c*), which later on becomes impregnated with calcareous salts. The osteoblasts come to lie in irregular spaces with processes (Fig. 138, *c*, and Fig. 139, *b*) which are generally called bone-corpuscles. In extensive development of cellular embryonic tissue, its transformation into bone always is limited to a part of the tissue, so that within the embryonic tissue trabeculæ (Fig. 138, *c*) are formed, which are called **osteoid trabeculæ** as long as they remain incomplete and do not contain lime-salts. The tissue between (*b*) is transformed into **marrow** by the cells becoming united to one another by processes, while there appears between them a fluid basement substance with scanty fibrillæ, in which, later on, round cells become embedded. If only a little bone is to be formed and old bony trabeculæ are to be coated over, then osteoblasts form a layer on its surface (Fig. 139, *c*), and these, later on, produce bone in the above-described way.

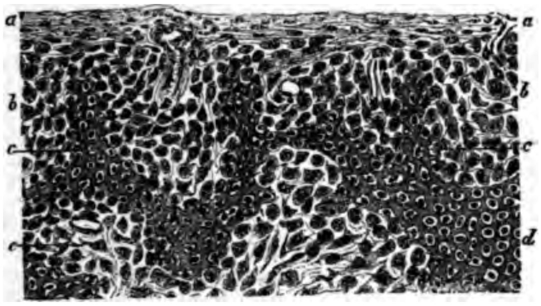

FIG. 138.—Formation of osteoid trabeculæ from the proliferating periosteum. *a*, Fibre layer belonging to the outer periosteum; *b*, Embryonic tissue; *c*, Osteoid tissue; *d*, Cartilage-tissue; *e*, Marrow. (Preparation from a fracture fourteen days old, hardened in Müller's fluid and alcohol, decalcified in picric acid, stained with hæmatoxylin and carmine, and mounted in Canada balsam. Magnified 50 diameters.)

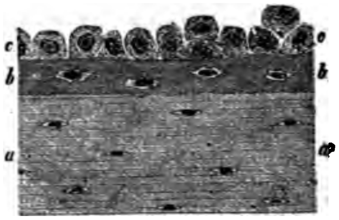

FIG. 139.—Bone-formation by heaping up of osteoblasts upon old bone. *a*, Old bone; *b*, New-formed bone; *c*, Osteoblasts. (Preparation hardened in Müller's fluid and alcohol, decalcified by picric acid, stained with hæmatoxylin and carmine, and mounted in Canada balsam. Magnified 300 diameters.)

Mucous tissue develops from embryonic tissue by the formation of a homogeneous, gelatinous matrix containing mucin and lying between the cells, while the latter, at least in part, form a network by means of processes.

Lymphadenoid tissue develops from embryonic tissue by the formation of a part of the cells into a supporting reticulum, while lymphatic round cells gather in the meshes of this network, which contains fluid. In injuries of lymph-glands there occurs, according to Ribbert, a regeneration by proliferation of the cells of the reticulum and of the vessel-walls, of the endothelium of the lymph-channels, and also of the cells of the lymph-nodes and cords already proliferating under normal conditions. The progeny of the cells of the supporting substance form a network in the meshes of which proliferating cells collect.

Fatty tissue arises by the taking up of fat into the cells of embryonic tissue or of a mucous tissue or connective tissue, while the cells change to fat-cells by the running together of the fat-drops which they contain.

The **basement substance** of the tissues described is **a product of the protoplasm of the formative cells.** Whether in the process parts of the protoplasm are directly changed into basement substance, or whether they secrete the basement substance or manufacture it from the intercellular fluid, are questions difficult to decide; yet it is probable that only the two first-mentioned methods of formation occur (cf. Fig. 135, *d*, and Fig. 136). At any rate, a consumption of albuminoids takes place, and in the course of the development of the matrix the formative cells become smaller. It is possible that part of them may be entirely consumed in the formation of the basement substance.

Fibrillated connective tissue can develop from any connective tissue that undergoes proliferation, by means of an embryonic tissue-stage.

Bone arises most often from periosteum, perichondrium, and marrow, but can take origin at times also from other connective-tissue structures, as, for example, intermuscular connective tissue.

Cartilage arises most often from proliferating perichondrium, periosteum, marrow, and cartilage itself, but occurs also in other connective-tissue structures—for example, in the connective tissue of the testis and the parotid. The cartilage-cells near a lesion may, under certain circumstances, by proliferation produce a large-celled embryonic tissue, but this does not reach any considerable size. In enchondroma the cell-multiplication and the new formation of cartilage take place in the same way as in physiological cartilage-growth. Very often the cartilage formed under pathological conditions is only a transitional tissue and changes very soon again into bone and marrow or into connective tissue (cf. Pathological Anatomy of the Bones).

New lymphadenoid tissue may develop as well from lymphadenoid tissue as from adipose tissue (Bayer) and fibrillate connective tissues, and occurs in the last case most often in the connective tissue of the mucosa and submucosa of the intestinal tract, as well as in the glandular organs; rarely in intermuscular connective tissue.

Mucous tissue may develop from all proliferating connective tissue, but appears only rarely in large masses, and is also for the most part a transitional form, which changes into adipose or connective tissue.

Adipose tissue develops in those situations which already normally contain fat, but occurs also at times in other places—for example, in the reticulated framework of atrophic lymph-glands, in the perimysium internum of atrophied muscles, etc.

The near relationship of the different forms of connective tissue to one another enables the various forms to pass from one to another without the need of an intermediate embryonic tissue-stage. Further details of this are contained in the next chapter.

§ 92. The **new formation of the white blood-cells** occurs, in the first place, within the lymphadenoid tissue of the lymph-glands, spleen, and intestinal tract, and the lymph-nodes contain areas distinctly separated off from their surroundings, in which there are always a large number of nuclear-division figures which belong for the most part to free cells. These areas are called *germ-centres* (Flemming). Moreover, proliferation of leucocytes by division occurs also in the lymph-channels of the lymph-glands and the tissues, and now there is no doubt that the leucocytes also undergo division in the circulating blood and in the tissue-spaces.

The division occurs first of all by mitosis; but amitotic division also takes place, and upon this phenomenon depends the fact that a large part of the leucocytes contain broken-up portions of nuclei, of peculiar lobulated or wreath-like shapes.

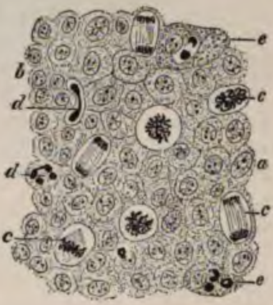

FIG. 140.—Section from the centre of development of a mesenteric gland (from Flemming). *a*, Large leucocytes; *b*, Small leucocytes; *c*, Karyomitoses; *d*, Direct division of the nucleus, or nuclear fragmentation, the significance of which is still unknown; *e*, Cells which contain, about the nucleus, large bodies that stain and smaller yellow pigment granules whose meaning is unknown. (Preparation treated with Flemming's acid-mixture and stained with safranine and gentian violet. Magnified 400 diameters.)

Mitotic division is the one which leads to the formation of viable cells. In how far amitotic division (fragmentation of the nuclei) is followed by cell-division is hard to tell, but there is no doubt that the leucocytes with broken-up nuclei represent for the most part elements undergoing retrograde metamorphosis. Consequently the transformation of uninuclear into multinuclear leucocytes would have to be regarded as an evidence of their death.

Not infrequently in pathological conditions an *increase in leucocyte-formation* takes place, and this may occur not only in the germ-centres, but also in other situations. This increase may lead to a temporary increase of the leucocytes of the blood—to a *leucocytosis*—as, for example, in the course of many infectious diseases, as pyæmia, erysipelas, pneumonia, pleurisy, peritonitis, in which especially the polynuclear cells are increased in number. It must, however, be noted that an increase of the leucocytes of the blood is no proof of an increased production, for the cells may be transferred from the lymphadenoid tissue into the blood in larger numbers. In the chronic disease called *leucæmia*, the eosinophile cells of the blood are increased, and there appear in this fluid mononuclear white and red cells which are not normally present in the blood. Since in leucæmia sometimes the spleen, sometimes the lymph-glands, sometimes the marrow, and in some cases all these organs together, show a condition of hypertrophy with increased cell-production, it is likely that the leucocytes present in the blood also for the most part come from these organs. Large mononuclear forms with neutrophile granules are characteristic of myelogenic leucæmia (Ehrlich). In the lymphatic and splenic forms the uninuclear lymphocytes are increased.

The **new formation of the red blood-cells** occurs (Bizzozero, Neumann, Flemming) by mitotic division of nucleated young forms of red blood-cells. In adult men the seat of this growth is limited to the bone-marrow, and this also holds good (Bizzozero) in the case of mammals, birds, reptiles, and tailless amphibia, while in tailed amphibia and in fishes the spleen also has a share in it. In embryos the development and multiplication of red blood-cells takes place in the entire vascular system; later, it is limited to the spleen, the liver, and the marrow, and finally to the latter alone.

Neumann claims that the multiplication of the young forms of the red blood-cells takes place in the lymphoid marrow, without more definitely indicating the situation. According to Bizzozero and Denys, it takes place only within the vessels of the marrow, and the complete development of the red cells is carried out in the same situation. The transformation of the nucleated into non-nucleated cells takes place, according to most observers, by disappearance of the nucleus. Rindfleisch and Howell hold that the nucleus passes out of the cell. According to Malassez, the cell separates off from the nucleus.

The origin of the nucleated red cells has not yet been satisfactorily explained. According to Bizzozero, the young red corpuscles are cells of a peculiar kind which always contain hæmoglobin and have no colorless periphery. Denys, Löwit, and Howell, on the contrary, assume that they arise from nucleated colorless cells without hæmoglobin, which, according to Denys, proliferate within the vessels of the marrow, while Löwit believes that the colorless antecedents of the red cells, dividing by mitosis, and which he calls erythroblasts, occur as well in the lymph-glands and spleen as in the marrow, and as well in the vessels as in the meshes of the reticulated tissue.

Flemming, who agrees with Bizzozero regarding the hæmoglobin of the nucleated young red blood-cells, is inclined to assume that the young forms which are present in later life are direct descendants of those of the embryo period, while Neumann believes that this hypothesis is not sufficient to explain all the phenomena of later life, as, for example, the replacing of the fatty marrow containing no nucleated red cells by blood-forming lymphoid marrow, and the formation of blood in entirely newly produced marrow. He finds himself driven to the assumption either that a development of the nucleated blood-cells takes place from the leucocytes of the blood which are carried to the marrow after birth by the arteries, or that the cells arise from the tissue-elements of the marrow.

In the increased blood-formation which takes place after loss of blood, as well, also, as in severe chronic anæmias and in leucæmia, nucleated red blood-cells occur also in the circulating blood outside the marrow, while under normal conditions they are not found there. The fatty marrow acquires in this way once more, in part, the character of lymphoid marrow, and this transformation is completed by disappearance of the fat, by a widening of the blood-vessels with an increase in their contents, and by an increase in the number of the colorless corpuscles of the marrow.

Ehrlich[*] and Einhorn[†] distinguish among the leucocytes of the normal blood: (1) *small lymphocytes* with relatively large nuclei that stain deeply, and with little protoplasm; (2) *large lymphocytes* with large nuclei that stain faintly, and with more protoplasm; (3) *mononuclear transition forms* with irregular nuclei; (4) *polynuclear neutrophile leucocytes* with polymorphous nuclei, or with several nuclei and neutrophile granules (granules which stain with a neutral dye, obtained by mixing acid fuchsin with basic methyl green), these forming about 70 per cent. of all the white cells of the blood, and migrating in purulent inflammations; and (5) *eosinophile cells*, whose protoplasm contains numerous granules which stain with acid dyes (eosin).

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[*] *Zeitschrift für klin. Med.*, i.; *Charité-Annalen*, 1884; *Verhandl. der Phys. Gesellsch. zu Berlin*, 1878–79; and *Deutsche med. Wochenschr.*, 1883.

[†] "Ueber das Verhalten der Lymphocyten zu den weissen Blutkörperchen," I.-D., Berlin, 1884; *ref.* "Fortschritt der Med.," iii.

According to Quincke, the life of a red blood-cell is probably about two or three weeks; but this estimate seems too small in view of some other observations, which indicate that a dog manufactures about 20 grammes of blood a day. As soon as the red cells are incapable of performing their function they are taken up by white blood-cells and eliminated from the blood-current, and this takes place by preference in the spleen and liver as well as in the marrow and lymph-glands. The red cells inclosed in the colorless cells (pulp-cells, marrow-cells), or their degeneration-products, are changed to colored or colorless iron compounds, which may be demonstrated microchemically sometimes in soluble, sometimes in granular form. A part of these iron compounds is later on taken up into the blood in the spleen and marrow, and probably also in the liver, and is used again in the formation of new red blood-cells. Another part of the iron, on the contrary, is excreted through the liver-cells.

Löwit distinguishes two separate forms of colorless blood-corpuscles, leucoblasts and erythroblasts, which, he thinks, have an entirely different meaning and do not pass from one form into the other. The leucoblasts are the lymphoid cells with chromatin arranged in lumps, and which do not suffer division by mitosis, but are changed to multinuclear leucocytes by fragmentation of the nucleus. The erythroblasts are the colorless youthful forms of the red blood-cells, which undergo mitotic division and differ from the lymphoid cells by the homogeneous character and slight contractility of the protoplasm. He claims that the transformation into cells containing hæmoglobin takes place partly in the blood, partly in the marrow.

Flemming considers Löwit in error, and claims that a transformation of colorless erythroblasts into red cells does not follow from Löwit's observations: he calls attention to the fact that nucleated red cells are generally absent, and that leucocytes that do not go on to form red cells suffer mitotic division. Neumann also is unable to agree with Löwit.

Howell claims that the marrow contains numerous colorless erythroblasts, which change in the marrow first into nucleated red cells, and, later on, into the non-nucleated form by extrusion of the nucleus.

Hayem is of the opinion that the red blood-cells arise from biconcave, non-nucleated discs, the blood-plates, which he accordingly calls hæmatoblasts. He considers that the blood-plates develop into colorless lymph-corpuscles, which are set free from the lymph before they come into the blood. Cadet and Pouchet hold opinions like the above, but the latter thinks that the nucleated red cells are formed by direct transformation of leucocytes. Malassez thinks they come from buds from nucleated cells of the marrow. According to Denys, with whom also E. H. Ziegler agrees, the red corpuscles have a peculiar origin. In birds they are formed from the wall of the venous capillaries of the bone-marrow, which have a germinal area for red cells, in the shape of a cellular coating of many layers, which gives up into the blood-stream cells which then come to contain hæmoglobin.

Foà and Salvioli advance the hypothesis that the large cells of the marrow, with central lobulated nucleus, produce red cells by the development of a bud from the nucleus, which comes to be surrounded by hyaline substance, then is constricted off, and finally comes to contain hæmoglobin.

§ 93. The **new formation of transversely striated muscle-fibres** starts from portions of old muscle-fibre; and if, after injury to a muscle, the intermuscular connective tissue goes on to active growth, it forms, later on, only connective tissue, or probably also the sarcolemma of the new fibres, but never new contractile muscle-fibres.

After injury of a muscle, the first signs of formative activity appear in the muscle-nuclei. These stretch out lengthwise and then (Steudel, Nauwerck) divide into a varying number of pieces. Already on the second day mitotic division of the nuclei may begin (Fig. 141, *a*, *b*), which seems to be the only way in which the tissue multiplies; and under favorable conditions this takes place quite actively after the second day.

The behavior of the contractile substance of the muscle differs very materially according to the nature and extent of the injury. In the case of traumatic, as well as of toxic and ischæmic injuries, it suffers fragmentation into larger and smaller portions, so that the muscle-cells come to lie in spaces of various sizes in the midst of the débris of the muscle-fibres. Crushing and tearing can bring about a wide separation of the parts of contractile substance. The ends of the pieces of fibre then become sometimes pointed, sometimes oblique, transverse, or with irregular edges. Not infrequently, also, after a short time, the ends become split into several pointed filaments (Fig. 141, *a*).

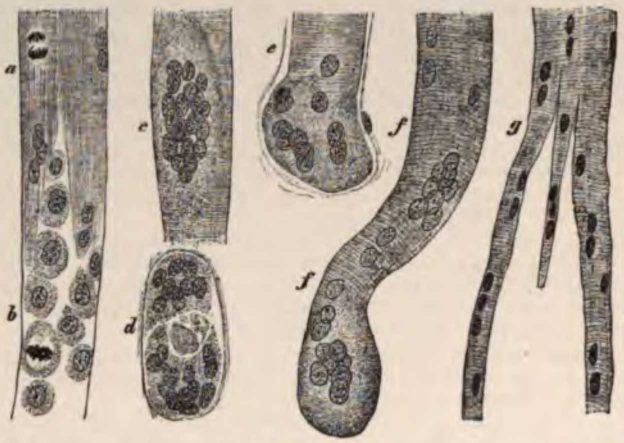

FIG. 141.—Portions of muscle-fibre, from wounds of muscle at various stages of regenerative growth. *a*, Pointed ends of a muscle-fibre with nuclear-division figures, three days after being torn across; *b*, Proliferated muscle-nuclei transformed into cells rich in protoplasm, of which one is in process of mitotic division; *c*, Piece of a muscle-fibre eight days after tying across a muscle; *d*, Giant cells which inclose a necrotic piece of muscle, from a muscle-cicatrix twenty-six days old; *e, f*, Muscle-fibres ending in masses of protoplasm (muscle-buds)—*e* from a ten-days-old, *f* from a twenty-one-days-old cicatrix; *g*, Muscle-fibre dividing, from a forty-three-days-old cicatrix. (Preparations hardened in Flemming's acid-mixture, stained with safranine, and mounted in Canada balsam. Magnified 350 diameters.)

The mitotic division of the muscle-nucleus takes place not only in the case of nuclei that rest upon living fibres (*a*), but also in the muscle-cells (*b*) lying free in the spaces between the fibres that have separated from one another, and is followed in both cases by the development of large multinuclear cells, which lead to the formation of multinuclear protoplasmic masses on the ends of the muscle-fibres (*e, f*), as well as in the body of the fibres (*c*). Between these and the transversely striated muscle-substance there is no sharp line of demarcation. There occurs, therefore, *with multiplication of the nuclei, a growth of the sarcoplasm of the muscle-fibres, and this becomes clearly visible*; and it is probable that the muscle-fibrillæ also may suffer a transformation again into sarcoplasm.

The muscle-cells that are not connected with living contractile substance become transformed into *large epithelioid cells with a large nucleus* (*b*), which again is changed, by continued nuclear division, into *multi-*

nuclear masses of protoplasm (*d*); and a cicatrix of from eight to thirty days, consisting of growing connective tissue, may possess such giant cells in large number, which often contain (*d*) débris of the old fibres.

The *new muscle-fibres are developed from the sarcoplasm rich in nuclei* which appears in the continuity and at the ends of the muscle-fibres, and is associated with the formation of numerous large nuclei; and by its increase in bulk it forms a growth in the muscle, which has been called *bud-formation* by Neumann. With the transition of the sarcoplasm into muscle-fibrillæ there appears gradually a longitudinal and, later on, also a transverse striation, an indication that the organic structure of the plasma has completed its development in the way characteristic of muscle.

The greater part of the *muscle-cells growing without connection with living muscle-fibres* die. Yet it must be noted that they last a long time, so that in many muscle-cicatrices of eight to forty days one can often find large numbers of masses of protoplasm rich in nuclei, which, under some circumstances, may form long continuous bands or whole rows of separate pieces of protoplasm. There is also no doubt that a part of these cells are, under favorable circumstances, transformed into transversely striated muscle-substance; and this occurs either by the formation of independent new muscle-fibres, or by union with old muscle-fibres or muscle-buds. According to Volkmann, the non-continuous muscle-growth takes place by preference when the contractile substance is destroyed, without destruction of the protoplasm itself—for example, in typhoid fever—while the budding is observed after cutting through of the muscle.

The buds springing from their ends or from their sides may form a simple prolongation of the muscle-fibre, frequently deviating from its original direction (*f*). Often there occur fibres split up into two or three parts (*g*), so that the old fibres branch as they pass into the muscle-scar. As far as we know, this splitting up occurs very early—often, indeed (*a*), before the proliferating muscle-nuclei have formed much sarcoplasm—so that the proliferation appears first in the products of the division of the fibres. As a result of this fission, cicatrices in muscle often contain a larger number of muscle-fibres than were originally present in the area in question.

The regeneration of muscle-tissue after injury requires favorable conditions as far as nourishment is concerned. Active inflammatory processes hinder it. On the contrary, nerve-influences are not essential to it, and consequently it takes place even if the corresponding nerves are destroyed.

Hypertrophy of striated muscle takes place by enlargement of the separate muscle-fibres, and yet a proliferation of the fibres may also be associated with this.

A **new development of cardiac muscle** seems to occur only to a very limited extent. To be sure, after injuries to the heart, nuclear-division figures may appear in the muscle-cells. Nevertheless, even after a few days, these can no longer be demonstrated, and the wound heals with ordinary scar-tissue. Foci of degeneration of the cardiac muscle heal in the same way by cicatricial connective tissue. If the **heart-muscle** is for any reason **hypertrophied**, this increase in size takes place by enlargement of the muscle-cells; whether or not a proliferation of the cells also is present is not yet positively known.

A **new formation of smooth muscle** occurs, as does regeneration, after traumatic or toxic and ischæmic degeneration. It occurs also in hypertrophic new formation of muscle-tissue—for example, in tumors—and is initiated by a mitotic division of the nuclei of the muscle-cells, which is followed by cell-division. According to both experimental work and observations upon the muscle-tissues of man, the reproduction of the fibres is slight, while after injuries and focal degeneration it ceases again after a short period. Thus, for example, defects in the muscularis of the stomach and intestine or of the bladder are repaired, for the most part, only by connective tissue. New muscle-tissue probably arises only from old muscle-tissue.

Hypertrophy of the smooth muscle-fibres is a phenomenon which, within certain limits, very often occurs. In the gravid uterus the size of the muscle-cells reaches five to ten times the ordinary. Of the other organs, the bladder most often shows a considerable hypertrophy of its smooth muscle.

§ 94. **Regenerative new formation of the nerve-elements of the central nervous system by new formation of ganglion-cells,** as far as is known, does not occur in man and mammals in post-embryonic life. After injuries or focal lesions, to be sure, nuclear-division figures may appear in neighboring ganglion-cells, but these do not seem to lead to cell-division and new formation of ganglion-cells. According to the investigations of Stroebe, on the contrary, divided nerve-fibres may grow somewhat lengthwise, and this holds good for the fibres of the pyramidal tract and of the posterior roots, both of which, after being cut through, grow out into the cicatricial tissue which develops at this point, the former in a downward, the latter in an upward direction. But a complete restoration of the nerve-tissue does not occur, and a traumatic defect in the spinal cord is really replaced by connective tissue, partly by neuroglia. It is not yet known whether the loss of separate nerve-fibres of the brain and spinal cord may, under favorable circumstances, be entirely restored again by the growing out of the axis-cylinders—for instance, if the supporting tissue be left intact.

Regenerative and hypertrophic growths of the neuroglia are phenomena which frequently occur in morbid affections of the nervous system, and either follow close upon degenerative changes in the nervous elements or upon destruction of the neuroglia itself, or they appear without such antecedents, and then take their origin partly in the period of development. They lead to a multiplication of the spider- and brush-cells, and at the same time, also, to an increase in the fibrillary elements of the supporting tissue, and under some circumstances a thick feltwork of fine fibres (sclerosis) may be formed which no longer contain any nerve-elements.

Regenerative new formation of the nerve-fibres of the peripheral nervous system occurs very often, and is present in all those cases in which the continuity of a nerve-fibre is interrupted or partly destroyed by any influences whatsoever. For its accomplishment, however, it is necessary that the ganglion-cell whose process forms the nerve-fibre in question be preserved.

If a nerve has been divided by cutting, the axis-cylinders, as well as the medullary sheaths, in the distal portion, undergo degeneration, in the course of which the sheaths break up into granular débris, which is later on absorbed. During the destruction of the nerve-fibres the nuclei situated beneath the sheath of Schwann go on to grow with the formation of mitoses, and form cells rich in protoplasm, which may take up into themselves the products of the destruction of the nerve-fibres (Stroebe).

Of the central portion of the nerve only the peripheral extremity degenerates, up to the next Ranvier's node, or the next but one.

The regeneration of the nerve begins a few days after the operation, in the proximal portion, and, indeed, according to Ranvier and Stroebe, in the very neighborhood of the incision; according to Vanlair, on the contrary, at a distance of from 1.5 to 2 cm. from it.

The first change consists in a swelling of separate axis-cylinders in the peripheral parts of the nerve-bundles of the central portion, which is later on followed by a splitting off of from two to five or more new axis-cylinders. The new axis-cylinders arising from the splitting up of the old ones grow in a longitudinal direction (Fig. 142, *a*, *b*), and form, within the sheath of Schwann, whole bundles (Fig. 142, *c*, and Fig. 143, *e*) of new nerve-fibres, which for the most part fill the entire lumen of the old nerve-tubes, and, indeed, stretch it, and, more rarely, also inclose remains of the old fibres (Fig. 143, *f*). According to Vanlair, they may even break through the old sheath of Schwann, and then either go on further in the endoneurium, or push through the perineurium of the nerve-bundles into the epineurium.

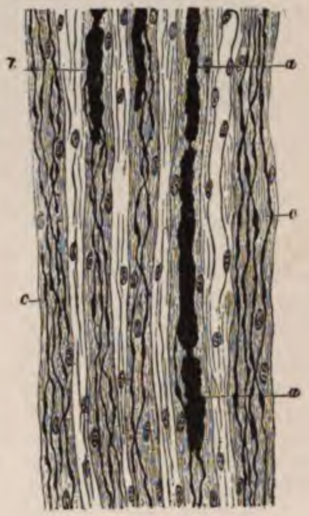

FIG. 142.—Old and newly formed nerve-fibres, from an amputation stump, in longitudinal section. *a*, *b*, Old nerve-fibres, from which several young nerve-fibres have grown; *c*, Neurilemma, with young nerve-fibres. (Preparation hardened in Müller's fluid, stained by Weigert's method (medullary sheath stained black), and mounted in Canada balsam. Magnified 200 diameters.)

In this way there are formed, on the lower end of the proximal portion of the nerve, a large number of new nerve-fibres, which originally consist only of the newly formed axis-cylinders, but immediately (Stroebe) surround themselves with a medullary sheath which, by reason of the irregularity of its development, gives to the nerve-fibres a varicose appearance (Fig. 142, *c*). Later, the fibres acquire a neurilemma sheath—that is to say, a connective-tissue shell, which probably is formed from the nerve-corpuscles concerned in the growth.

If a nerve is entirely severed, and with no possibility of a union of its cut ends—as, for example, occurs in all amputations of extremities—then there is developed in the region of the cut end a germ-tissue springing from the connective tissue of the nerve, which later on changes into connective tissue. Originally free from nerves, this connective tissue becomes traversed by young nerves which grow out from the nerve-stump, and which, arranged in small bundles, or scattered, grow into the cicatricial tissue and pierce it in every direction (Fig. 144). Often the growth of nerves is so extensive that knob-like or clubbed swellings—known as *amputation* neuromata—arise on the ends of the nerves (Fig. 144).

If a nerve is divided, but, after the division, has been again united, or if the division has been incomplete, the nerve-fibres which grow out from the proximal portion, piercing through the connective tissue which is formed in the neighborhood of the wound, may in part, or all, find their way into the peripheral portion, where, in the meanwhile, the nerve-fibres have perished.

Fig. 143.

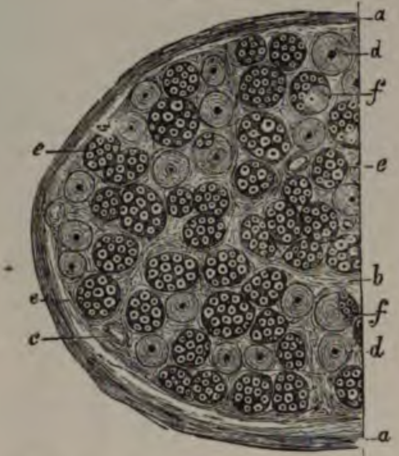

FIG. 143.—Cross-section of a nerve-bundle of the median nerve, just above a wound made four months previously. *a*, Perineurium; *b*, Endoneurium; *c*, Cross-section of a vessel; *d*, Old unchanged nerve-fibre; *e*, Bundle of newly formed nerve-fibres; *f*, Newly formed nerves, with remains of the old fibres inside the same sheath. (Preparation hardened in Müller's fluid, stained with neutral carmine, and mounted in Canada balsam. Magnified 200 diameters.)

Fig. 144.

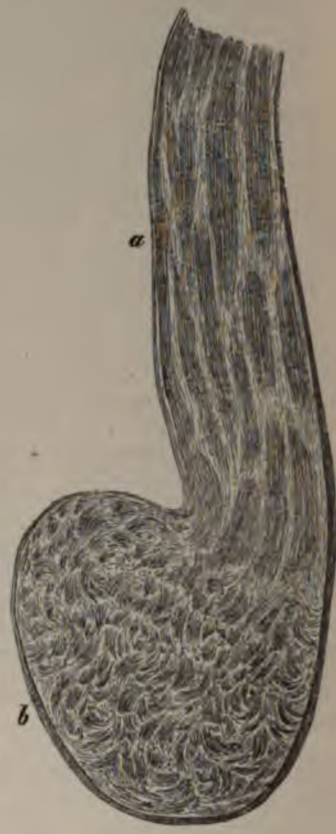

FIG. 144.—Amputation neuroma of sciatic nerve in longitudinal section (amputation of the nerve nine years before). *a*, Nerve; *b*, Neuroma. (From a preparation hardened in Müller's fluid. Magnified 3 diameters.)

According to the investigations of Vanlair, the growth of a nerve in process of regeneration amounts to 0.2–1.0 mm. per day, according to the nature of the tissue in which it lies. Single young nerve-fibres may burrow into the old empty sheaths of Schwann (Vanlair), but the majority of them press into the epineurium (Vanlair) and perineurium, and in this situation grow toward the end-organs. Separate fibres also pass by the ends of the nerves, and grow toward the periphery either along the old nerves, or by an independent route of their own. Finally, many fibres which have left the old route are lost in the tissues. In the lower half of the intermediate portion the nerve-strands have already begun to separate into bundles again, and with the formation of a perineurium about the latter, the regenerated nerve may take on more and more the structure of a normal nerve.

The above-described process of regeneration requires for its accomplishment weeks or even months, and sometimes is not complete even after several months. According to Eichhorst, toward the end of the first month, generally, the fibres of the central trunk have pierced the cicatrix. In the course of the third month, usually, the regeneration is complete.

As is evident from the description, the peripheral portion of a divided nerve is not regenerated from itself, but is furnished with nerve-fibres from the central portion. Vanlair calls this *neurotization*. This process is repeated in all cases in which a divided nerve is regenerated, and, indeed, even if the severed nerves are united immediately, or if only the nerve-fibres and not the connective-tissue structures are divided. The difference between the two cases consists in this only: that in the first instance the young nerve has to grow through a tolerably extensive area of embryonic and cicatricial tissue, while in the latter case this intermediate area is absent, or, at least, is very thin, so that the growing axis-cylinders are entirely within the nerve.

The views of different authors concerning the formation of axis-cylinders in severed nerve-fibres are very diverse. Waller, Schiff, Rindfleisch, Cornil, Ranvier, Eichhorst, Vanlair, and others believe that it occurs through a longitudinal fission of and an outgrowth from the old axis-cylinders of the central portion. According to Philippeaux, Vulpian, Remak, Leegard, Neumann, Dobbert, Daszkiewicz, and others, the new fibres originate in the peripheral end, and, indeed, according to Leegard, from the nuclei of the neurilemma; according to Remak, by longitudinal division of the old axis-cylinders that have remained intact; according to Daszkiewicz, from the remains of the old axis-cylinders broken up transversely; according to Neumann and Dobbert, from a protoplasmic mass which has developed in advance by a chemical metamorphosis of the medulla and the axis-cylinder. According to Cattani, new axis-cylinders develop in degenerated nerves in the interior of a nucleated protoplasmic mass which, in the degenerated fibres, fills the sheath of Schwann.

Nasse, Günther, Schön, and Steinbrück claim that the axis-cylinders originate from the old fibres of both ends; Leut, Einsiedel, Weir Mitchell, Beneke, Gluck, and von Büngner, that they come from the nuclei of the sheaths of Schwann of both portions; while, according to Laveran and Herz, they spring from white blood-corpuscles; finally, Hjelt and Wolberg think they arise from the cells of the perineurium.

Those authors who are of the opinion that after nerve-division the axis-cylinder in the peripheral portion remains intact assume also that, in regeneration, a reuniting of the central and peripheral axis-cylinders takes place by means of an intermediate piece. Wolberg holds that this takes place by means of strands of spindle-cells which arise from the perineurium. He believes, however, that also a healing by first intention is possible, in the sense that the cut surfaces of severed axis-cylinders and sheaths of Schwann are immediately united.

According to my observations upon regenerating nerves, the process of regeneration as it is above described is firmly established. I am supported partly by my own observations, partly by those of Stroebe, whose admirable preparations, in my opinion, admit of no other interpretation.

III. Metaplasia of the Tissues.

§ 95. By **metaplasia** of a tissue is understood a process by which *an already completely formed tissue is transformed into another* without a cellular intermediate stage—that is, an embryonic tissue or formative tissue. Such a transformation occurs only in structures that are closely related to one another, especially, therefore, in the connective tissues. In this group, under pathological conditions, all the forms may be transformed one into another without the appearance of any intermediate growth—a phenomenon which is not startling, for, indeed, it occurs normally. If mucous tissue is changed to adipose, then the star-shaped tissue-cells change to round adipose cells by taking up fat, while the mucous basement substance disappears. In the same way, lymphadenoid tissue, after disappearance of the lymphatic elements, may change to adipose tissue by the taking up of fat in the cells of the reticulum. The cellular and gelatinous bone-marrow also behaves in the same way.

By disappearance of the fat, adipose tissue may take on the appearance of mucous tissue, and at times, also, may contain nuclei. If the basement substance of hyaline cartilage becomes fluid, so as to form a mucilaginous jelly, or if it becomes completely dissolved, then the cartilage-cells (Fig. 145, *a*) set free in this way change to stellate cells anastomosing with one another (*c*, *b*), so that a tissue is formed which corresponds in its structure to mucoid tissue or to the reticular tissue of bone-marrow. By taking up of fat the latter may become adipose tissue; by storing up of round cells in its meshes it becomes cellular marrow-tissue. If the basement substance of hyaline cartilage becomes fibrous, and if it changes at once to a glue-producing material, then connective-tissue cartilage is produced. If the cartilage-cells lose their characteristic nature, and if they become flat connective-tissue cells, then the cartilage changes into ordinary connective tissue.

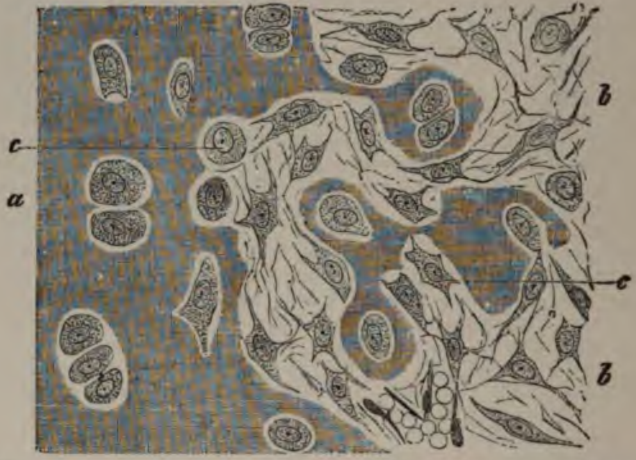

FIG. 145.—Metaplasia of cartilage in reticular tissue, in arthritis fungosa. *a*, Hyaline cartilage; *b*, Tissue consisting of branching cells; *c*, Cartilage-cells set free by solution of the cartilage basement substance and passing over into mucous-tissue cells. (Magnified 400 diameters.)

If portions of the cartilage change to medullary tissue, then other parts of it may at the same time be transformed into bone, in which case the basement substance is changed into a gelatinous material and impregnated with lime-salts, while the cartilage-cells are transformed into bone-cells, in the neighborhood of which the basement substance of the bone forms the bone-corpuscles. If connective tissue changes directly into bone (Fig. 146), then in the first place a condensation of the basement substance (*b*) takes place, and later on a storing up of lime (*c*), in the course of which the connective-tissue cells (*d*) come to lie in indented spaces or bone-corpuscles and become bone-cells (d_1).

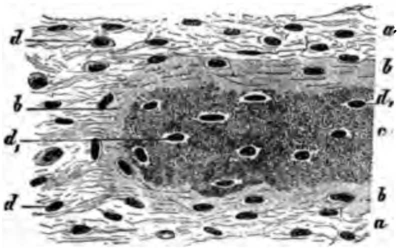

Fig. 146.—Bone-formation from connective tissue. Cross-section through a bone-trabecula in process of formation from an ossifying fibroma of the periosteum of the upper jaw. *a*, Connective tissue; *b*, Thickened tissue, forming the groundwork of the new bone; *c*, Lime-deposit; *d*, Connective-tissue cells; d_1, Bone-corpuscles. (Preparation hardened in alcohol and cut without decalcifying, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 200 diameters.)

If connective tissue is to be transformed into mucous tissue, then the fibrillæ disappear, and there appears in their place a gelatinous mucus. If numerous lymphatic round cells establish themselves in a fibrillated connective tissue, and if at the same time a breaking up or a disappearance of the connective-tissue fibres takes place, while the connective-tissue cells persist, and unite to form a reticular tissue by the development of processes, then in this case a lymphadenoid tissue may be developed from it.

Metaplasia of connective tissue is to be distinguished not only from simple degeneration, but also from the processes of growth. From the former no new tissue arises, but the old tissue perishes. In the latter it is a question of a new tissue, rich in cells, and taking its origin in cell-division. Metaplasia stands, in a certain sense, midway between the two. A new tissue, to be sure, is formed, but cell-growth is not present, or at least is a minor matter.

In many ways the process is allied to the retrogressive changes; for example, the change into mucous tissue is a process very similar to mucous degeneration. Moreover, the new tissue is not infrequently a perishable one. On the other hand, one often enough observes developmental processes following upon metaplasia. Sometimes the condition of the blood-vessels has the greatest influence upon the subsequent course of events, since a good vascular supply for the tissue suffering metaplasia favors a further development of it, while its absence, on the contrary, encourages retrograde metamorphosis.

In mucous membranes the seat of chronic inflammation—for example, of the uterus and the respiratory tract—it not rarely happens that the cylindrical epithelium in places changes to pavement epithelium, a phenomenon which is known as *epithelial metaplasia*. The transformation takes place in this way: the regenerating epithelium changes its character after repeated loss of the original epithelium. In the stratified pavement epithelium of a mucous membrane, moreover, a *horny degeneration* of the upper layer of cells may take place, and, indeed, not only in situations which normally possess pavement epithelium—for example, in the urinary passages—but also in those where it has developed pathologically, as in the nose and uterus.

SECTION VI.

Inflammation and the Associated Processes of Repair.

I. Acute Inflammation and its Various Forms.

§ 96. **Inflammation** is essentially a **local tissue-degeneration combined with pathological exudations from the blood-vessels**, caused by some injurious agency, with which are associated, sometimes earlier, sometimes later, *tissue-proliferations* leading to regeneration or to hypertrophy.

In acute inflammation the exudation is generally associated with a pronounced hyperæmia, which begins even before the exudation, and introduces it. As a result of the combination of hyperæmia and exudation, the inflamed tissue is reddened and swollen. If it is situated on the surface of the body, where the tissues are cool, the increased supply of warm blood from the deeper parts produces local increase of temperature. If the tissue contains sensory nerves, the sensation of pain sets in at the same time with the changed conditions in the inflamed area.

Redness, swelling, increased heat, and **painfulness of the inflamed tissue** are phenomena which even in antiquity the physicians regarded as signs of inflammation; and **rubor, tumor, calor,** and **dolor** were designated by Celsus, at the beginning of our era, as the **cardinal symptoms of inflammation.** To the four was then added a still further symptom —**functio læsa, altered function** of the inflamed tissue.

The **causes of inflammation** may be attributed to *mechanical, thermic, electrical, or chemical actions*, and also to the *influence of parasites*. It is a common characteristic of all these injurious agencies to produce at first a *local tissue-degeneration, which in a certain degree of extent and of intensity is associated with disturbances of the circulation and of the vascular secretion.* The causes of inflammation are not specific injurious agencies; but, rather, every injurious agency may produce inflammation, if, on the one hand, its action is sufficiently intense to induce certain disturbances of circulation with tissue-degeneration, while at the same time it does not act strongly enough to destroy the tissue and stop the circulation.

Most causes of inflammation reach the human organism from the outside, but excitants of inflammation may also be formed in the interior of the body. Bacteria which have penetrated into the tissues very often produce at first, from the substances present in the body, products whose action induces inflammation. Then, moreover, substances that excite inflammation can develop in the organism even without the aid of parasites; for example, if tissues die in large masses from any cause—e.g., as a result of ischæmia—or if, in consequence of disturbances of the processes of assimilation (gout), abnormal products of metabolism are deposited in the tissues.

The exciters of inflammation can act upon the tissues both from the external parts of the body and also from the lymphatics and the blood, and one can accordingly distinguish *ectogenous, lymphogenous,* and *hæmatogenous inflammations.* Through the extension of inflammations to the neighboring regions there arise *inflammations by continuity;* the transfer of the producer of inflammation from a focus of inflammation through the lymph- or blood-stream leads to *metastatic inflammations.* If noxious substances are discharged by the excretory organs, *excretory inflammations* may arise.

When a local injury to tissues has reached such a degree as to produce the exudation characteristic of inflammation, there is usually present a **congestive hyperæmia,** on account of which the blood flows with increased quickness through the dilated channel. After a short time there occurs, however, on the other hand, a lessening of the speed of the circulation, which ends in a **slowing of the blood-current.**

The first disturbances of the circulation, which find their expression in the congestive hyperæmia, can be due either to an irritation or a paralysis of the vaso-motor nervous system, or to a direct action on the walls of the vessels, particularly those of the arteries, which has as a result a dilatation of the channel. Although these very often precede the inflammatory exudations, they still form no essential characteristic of inflammation, but occur very often when an inflammatory exudate does not follow them. The circulatory disturbance characteristic of inflammation is shown only when the **slowing of the blood-current** and the **pathological exudation** from the vessels set in. As has been demonstrated, principally by the researches of Cohnheim, Samuel, and Arnold, the slowing of the blood-stream in the widened channel and the pathological exudation are caused by a *modification of structure,* **an alteration of the vascular walls**; while this induces both a lasting dilatation and an increase of the adhesion of the blood to the wall of the vessel, together with *an increase of resistance from friction,* and lastly *an increased permeability of the vascular walls.* In the capillaries the lasting dilatation is chiefly the result of *relaxation of the connective tissue surrounding them,* while the thinness of the capillary walls makes this tissue bear a great part of the pressure upon them.

The **tissue-lesion** which leads to the phenomena of inflammatory disturbance of circulation and exudation affects generally all parts of the tissue, but may, under certain conditions, be confined to the vascular walls, particularly when it is a case of hæmatogenous inflammation, in which the injurious agency acts from the blood. However, the tissue in the region adjoining the capillaries must soon become involved in associated suffering. The tissue-changes which are established by the excitants of inflammation are sometimes only transient, and not easily, or not at all, recognizable even by microscopical examination; at other times they are serious, so that they can be easily recognized even by macroscopic inspection. The latter is particularly the case when a considerable time has passed since the occurrence of the damage. In the subsequent progress there are often added to the lesions established by the causes of inflammation other tissue-changes, which are produced by the inflammatory disturbances of circulation and by the collection of exudate in the tissues.

If in any tissue the cause of inflammation has led to that alteration of the vessels which is the requisite antecedent of the inflammatory disturbance of secretion—i.e., the formation of inflammatory exudate—and if as a result of this there is already evident a slowing of the blood-current, the circulation in the capillaries is performed in an irregular way, and there is here and there stagnation, or transient or permanent cessation of flow. Since, in this event, the colorless blood-cells often remain attached to the walls, while the red blood-corpuscles are carried on, there occurs **in the capillaries** a more or less marked **increase of the colorless blood-corpuscles** as compared to the red. **In the veins,** in which one can distinguish in the normal circulation an axial red stream and a cell-less plasmatic peripheral zone, more or less numerous **leucocytes pass over into the peripheral plasmatic zone** when there is a certain degree of slowing of the circulation. Still greater slowing of the circulation results in the passing over of blood-plates and of red blood-corpuscles into the peripheral plasmatic zone, and finally the difference between the axial stream and peripheral zone may be entirely lost.

When leucocytes have passed over into the peripheral zone they either roll along further or attach themselves to the vein-wall, either to roll on again further after a time or to remain permanently attached. If this occurrence leads to a marked accumulation of leucocytes along the walls of the veins, the appearance is called **marginal disposition of the colorless corpuscles** (Fig. 147, *d*).

Related to the accumulation of leucocytes in the capillaries and to the marginal disposition in the veins is the *emigration of the leucocytes from the vessels* involved (Fig. 147, *d*, *e*), and there occurs simultaneously a *pouring out of fluid from the vessels.*

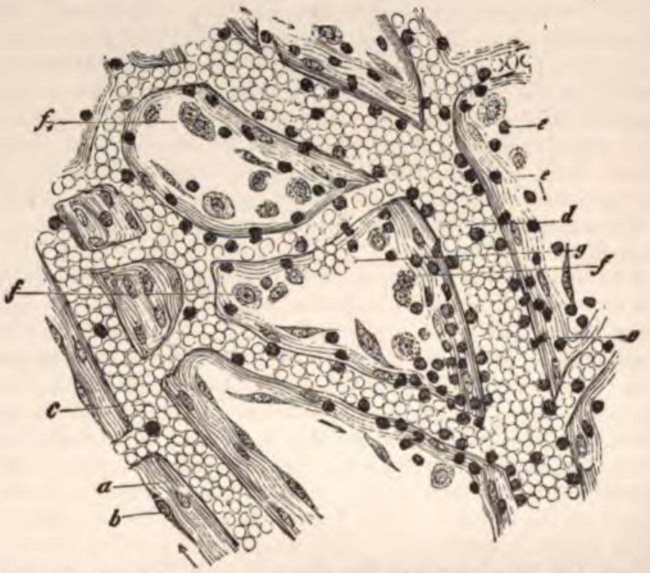

FIG. 147.—Inflamed human mesentery. *a*, Normal trabecula of mesentery; *b*, Normal epithelium; *c*, Small artery; *d*, Vein with peripheral colorless blood-corpuscles; *e*, Colorless blood-corpuscles, emigrated or emigrating; *f*, Desquamated epithelium; *f*₁, Polynuclear cell; *g*, Extravasated red blood-corpuscle. (Osmic-acid preparation. Magnified 180 diameters.)

The **emigration of the colorless blood-corpuscles** is an active process, which is accomplished by the amœboid movement of the cells, and it also occurs independently under normal conditions. The cause of the enormous outpouring, as it is observed in inflammations, is doubtless a change in the vessel-walls, which is favored by the circumstances that the leucocytes attach themselves to these walls and also pass through them. According to the researches of Arnold, Thoma, and others, the places where the wandering out occurs are the cement lines between the endothelial cells, and in the inflammatory vascular alteration a partial widening of these spots occurs. The emigration is accomplished in such a manner that the leucocyte first sends a process through the vessel-wall and then flows after the process with the rest of the cell-body, until finally the whole mass lies outside of the vessel. Arrived here, the leucocytes may remain stationary at first, but generally they wander further, when the direction of the excursion is generally settled by *chemotaxis*—i.e., the attraction or repulsion due to chemical substances present in solution in the tissue-juices. Possibly chemotactic influences sometimes exert an influence both on the leucocytes situated at the periphery and on those which are at a standstill in the capillaries. The leucocytes that have migrated from the vessels are chiefly polynuclear forms that make up about 70 per cent. of the colorless corpuscles in the blood. Their number is sometimes large, sometimes only small.

The **pouring out of the fluid exudate,** whose composition always varies more or less from that of the normal tissue-lymph and is distinguished by a relatively *high proportion of albumin*, is a process which is also to be referred to an *alteration of the vessel-walls*, in consequence of which *the secretory function of the latter suffers a disturbance.* It takes place simultaneously with the migration of leucocytes; may also, however, begin even before it, or occur in cases in which emigration of leucocytes is lacking or remains within very narrow limits. The *composition of the exudate* is dependent in every case partly on the peculiar property of the vessels affected—which always varies according to the formation of the tissue to which they belong—partly on the degree of vascular alteration; and it is to be admitted that the quantity of albumin is larger the more the vascular wall is injured. If the extravasated fluid contains fibrinogenous substances and fibrin-ferment, and if, on the other side, no influences opposed to such a change are acting, **coagulation**—i.e., a **separation of the fibrin,** which is generally deposited in the form of filaments and granules—may occur in the exudate.

If the alteration of the vessels is of a very high degree, or if at the same time the stasis is pronounced, **red blood-corpuscles may emerge from the vessels** along with the fluid, either by diapedesis or by rhexis. The diapedesis takes place, according to Thoma and Engelmann, especially at the places where leucocytes have previously passed through the wall of the vessel, and the escape of red blood-corpuscles by the same route may follow very quickly. Since the red blood-corpuscles are not motile, their escape must be regarded as a passive process which is performed under the influence of pressure within the capillaries.

The **escape of blood-plates** into the exudate can occur both in exudates which are rich and in those which are poor in cells, but occurs principally in exudates that are distinguished by their rich proportion of fibrin and red blood-corpuscles, while the leucocytes are fewer in number.

The clinical significance of the term *inflammation* (*phlogosis*) has, on the whole, changed little in the course of time, since the cardinal symptoms of inflammation brought forward by Celsus, and accepted by Galen, are recognized as such at the present day. Just so much the more do the views differ about the differentiation of the essential from the accidental in the symptom-complex of inflammation, and about the accurate determination of its real nature. A comparison of the expressions concerning these points on the part of recent authors (Virchow, von Recklinghausen, Cohnheim, Samuel, Thoma, Neumann, Stricker, Heitzmann, Grawitz, Leber, Metschnikoff, and others) shows that no single one defines inflammation in the same way as any other, or judges in exactly the same way the individual phenomena of inflammation. The definition which I have given above can accordingly not lay claim to universal recognition; yet since its advancement[*] it has met with no opposition, and I believe I may therefore dare to hope that it finds acceptance by other pathologists also.

Formerly one believed that one should discern in hyperæmia the most essential symptom of inflammation. Rokitansky maintained that every inflammation was characterized by a dilatation of the capillary vessels, slowing of the blood-stream, and stasis, which was caused by a thickening of the blood through the effusion of serum, and by an adhesion of the red blood-corpuscles one to another. Henle, Stilling, and Rokitansky attributed the dilatation of the vessels and the slowing of the blood-stream to a paralysis of the vessel-nerves, the cause of which, according to Henle and Rokitansky, is an increased excitement of the sensory nerves; while according to Stilling, the cause is a paralysis of these nerves induced by the inflammatory irritant. Eisenmann, Heine, and Brücke sought to attribute the disturbances of the circulation to a primary spasm of the vessels, which is brought about by irritation of sensory nerves, and which produces, behind the contracted places, slowing of the current, irregular circulation, and finally even stasis. Vogel, Emmert, Paget, and others, on the other hand, attributed the dilatation of the vessels and the stasis to an abnormal attraction of the tissues for the blood. In opposition to these opinions, however, one must maintain that all the changes of circulation produced by contractions and paralysis of the vessels certainly precede or accompany the inflammatory —i.e., the circulatory—disturbances which lead to the formation of exudate, and may have a modifying influence on the course of the inflammation, but that they do not belong to the essence of inflammation, and therefore may either be lacking or be present in it, without the accompaniment of inflammatory exudate.

Rokitansky sought to explain the pouring out of fluid from the vessels in inflammation by the assumption that with the dilatation of the vessels there occurred also a thinning and an increased permeability of the vascular wall. Vogel, C. Emmert, and Paget, on the other hand, made this phenomenon also dependent on an increased attraction between the blood and tissue parenchyma or juices. Virchow, on the other hand, believed (1854) that a part of the exudate—that which collects in the tissue-crevices and is poured out on the free surfaces of the body—is the result of mechanical pressure in the vessels—i.e., is pressed-out blood-serum; while a part, which is chiefly derived from the "irritated" cells, is to be considered as the product of an increased attraction on the part of the tissues for the blood-constituents. Of the cells that collect in the inflamed region, he believed that all originate from a proliferation of the tissue-cells occurring in consequence of the action of the inflammatory irritant.

The recognition that the formation of exudate is to be referred to an injury to the vessel-walls we owe chiefly to Cohnheim, whose researches in various directions were completed by Samuel, Arnold, Thoma, Binz, and others. Cohnheim also showed that in inflammation the colorless corpuscles emigrate and form an essential constituent of the inflammatory exudate.

Dutrochet[†] and Waller[‡] already in the years 1842 and 1846 had described the escape of colorless corpuscles from the circulating blood. The observation, however, fell into complete oblivion till Cohnheim rediscovered the occurrence in 1867.

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[*] Cf. Ziegler, "Historisches und Kritisches über die Lehre von der Entzündung," *Beitr. v. Ziegler*, xii., 1892.

[†] "Rech. anatomiques et physiologiques sur la structure interne des anim et des végétaux et sur leur motilité," Paris, 1842, p. 214.

[‡] *Philosoph. Magaz.*, xxix., 1846, pp. 271. 398.

As follows from the researches of Schklarewsky,* the peripheral disposition of the colorless blood-corpuscles in the veins is a purely physical phenomenon. If one makes liquid, in which finely pulverized substances of varying specific gravity are suspended, flow in tubes, at a certain degree of retardation of the current the specifically lighter bodies pass over to the peripheral zone; and when the rate becomes still slower, the heavier bodies also enter this zone.

For the emigration of the colorless corpuscles to occur, it is necessary, according to the researches of Binz, Thoma, and Lavdowsky, that they be capable of motion and of adhering to the vessel-wall. According to these authorities, therefore, the emigration of the colorless blood-cells is not a purely passive, but at least in part an active process. If one reduces the motility of the colorless corpuscles by irrigation of the mesentery with a 1.5 per cent. solution of salt (Thoma), or if one lowers their vital activity with quinine or iodoform (Binz, Appert, Kerner), the emigration is also inhibited. Pekelharing, on the other hand, believes that one should accept the view that quinine, oil of eucalyptus, and salicylic acid produce a narrowing of the veins, restrict the increase of permeability of their walls, and thus reduce the extravasation of colorless corpuscles; a view which is rejected, however, by Disselhorst, who observed a dilatation of the veins after irrigation of the tissues with quinine, carbolic acid, salicylic acid, and sublimate. As there occurs in this case a retardation of the current after a transient acceleration, without the emigration of the leucocytes that pass out into the peripheral zone; and as, on the other hand, leucocytes from blood-vessels that have been irrigated for an hour with quinine are still of complete vitality (Eberth), Disselhorst is of the opinion that the drugs mentioned so change the inflamed vessel-wall that an accumulation of the leucocytes that pass by either cannot occur at all, or can do so only with difficulty.

Very probably a lesion of the vascular wall is not absolutely necessary for the emigration of leucocytes (Thoma). Since vaso-motor disturbances of the circulation can produce migration (von Recklinghausen, Thoma), a slowing of the blood-stream, the ability of the colorless corpuscles to perform amœboid movements and to adhere to the wall of the vessel, and their disposition to remain in the peripheral zone of the stream, probably furnish all the conditions necessary for this migration. Possibly differences in the watery content of the tissues (Thoma) also exert some influence, since an increased amount of water increases amœboid movement. It is also possible that the presence in the tissue-fluids of substances having chemotactic action may lead to migration of leucocytes which remain attached to the inner wall of the vessel (*vide* § 105).

According to the researches of Arnold, Thoma, and Engelmann, a soft cement substance lies between the borders of the endothelial cells, and this substance suffers a change in the circulatory disturbances associated with cell-migration—a change which may sometimes be recognized in the histological examination in the form of numerous circumscribed widenings of these intercellular areas (Engelmann). If leucocytes pass through these parts of the vessel in large quantities, the cement substance becomes still more permeable, and soon permits red blood-corpuscles also to pass through in quick succession (Thoma).

Under normal conditions, wandering cells are found in many tissues (von Recklinghausen), and wander from there partly into the lymph-vessels (Hering, Thoma), sometimes also into the blood-vessels (Bubnoff, Schulin, Ranvier, Senftleben), or to the surfaces of mucous membranes, to which they penetrate between the epithelial cells. About collections of lymphadenoid tissue in the mucous membrane they may constantly be found in abundance, and wander from there to the surface through the epithelial layer. According to observations of Kunkel and Siebel, a few of them may also reach the free surface of the alveoli of the lungs.

The discharge of fluid from the capillaries and veins was regarded by Cohnheim and Hering as a process of filtration, which is modified in inflammation

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* *Pflüger's Arch.*, 1. Bd.

by the alteration of the vessel-walls in such a manner that a liquid abnormally large in quantity and rich in albumin transudes. According to the researches of Heidenhain, however, the formation of lymph is not a simple filtration process, but a *process of secretion*, which is caused by a peculiar property of the living vessel-wall; and accordingly the inflammatory exudate is dependent on a change of the functional action of the vessel-walls, especially of the endothelium (cf. § 44).

The inflammatory disturbances of the circulation and the formation of exudate may be most easily followed on the transparent membranes of the cold-blooded animals, especially on the mesentery or the extended tongue or the spread-out web-membrane of the frog. On the frog's mesentery, which has been spread out on a suitable object-stand, circulatory disturbances and inflammation develop from simple contact with the air and the drying that results; the tongue and the web-membrane must be cauterized in order to become inflamed. By the employment of suitable apparatus, the circulation of the blood and the formation of inflammatory exudate can be observed with the microscope on the thin membranes of mammals also (mesentery of rabbits, wing-membrane of bats), and observations made in this manner show that the phenomena which occur agree completely with those observed in the frog.

§ 97. The *cellular and fluid exudates* secreted by the vessels collect first in their neighborhood, but soon spread out in the vicinity, mass themselves in the *lymph-spaces of the tissues*, and thus form a **tissue-infiltrate** (Fig. 149, *b*, and Fig. 151, *p*). When the exudate is abundant, it can spread out and infiltrate also the neighboring sound tissue that has not been injured by the cause of the inflammation. This **infiltration** may be so considerable as to produce new disturbances of circulation and

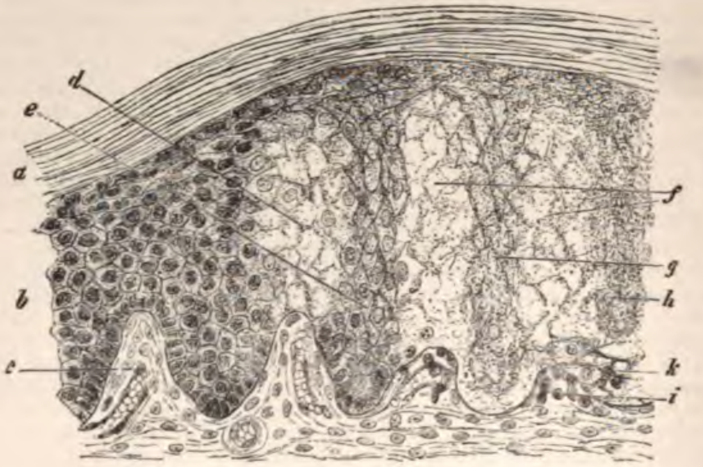


FIG. 148.—Section through the border of a blister. *a*, Horny layer of the epidermis; *b*, Rete Malpighii; *c*, Normal papillæ; *d*, Swollen cells, some of the nuclei of which are still visible, but pale, while others have been entirely destroyed; *e*, Interpapillary epithelial cells, the deep ones intact, while in the upper layers they are drawn out lengthwise and are somewhat swollen, without nuclei; *f*, Total liquefaction of the cells; *g*, Interpapillary cells without nuclei, swollen, and raised from the cutis; *h*, Total degeneration of the interpapillary cells which are separated from the cutis; *i*, Flattened papillæ infiltrated with cells; *k*, Coagulated exudate (fibrin) lying under the lifted epithelium. (Carmine preparation. Magnified 150 diameters.)

nutrition, and thus increase *the area of tissue-degeneration and inflammatory exudation.*

When *exudate* is present in a tissue, it *may be absorbed in part by the tissue-elements themselves,* so that they swell up and not rarely contain *drops of fluid,* which are ordinarily called *vacuoles.* There often occurs, also, a complete **dissolution of the tissue-elements** in the exudate, especially of the connective-tissue cells (Fig. 148, *d, f*), and not seldom, also, of the intercellular substance. In this way both brain- and muscle-tissue, as well as ordinary connective tissue, may be completely liquefied in the course of an inflammation.

If dead cells become saturated with lymph containing fibrinogen, and fibrin-ferment is formed, a **coagulation** may precede the liquefaction of the infiltrated tissue; in which case the cells are transformed partly into homogeneous masses without nuclei, and partly into granules and filaments (Fig. 150, *c, d*).

If the exudate within an organ—e.g., a gland—is chiefly in the supporting tissue, while the specific parenchyma appears little altered, the form of the inflammation is designated as an **interstitial inflammation** (Fig. 149, *b*). On the other hand, if the degeneration of the specific tissue—e.g., of the epithelium of the uriniferous tubules (Fig. 150, *c, d*) of the kidney, of the liver-cells in the liver, of the contractile substance in the muscles—is prominent, and these parts appear saturated with exudate, one calls the condition **parenchymatous inflammation.**

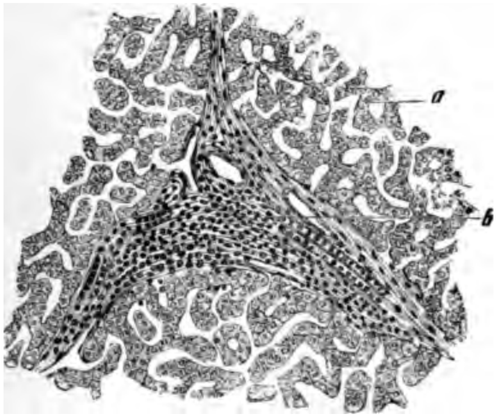


Fig. 149.—Recent interstitial hepatitis. *a*, Normal liver-tissue; *b*, Small-celled infiltration of the periportal connective tissue. (Hæmatoxylin preparation. Magnified 80 diameters.)

If the seat of an inflammation is the surface of an organ, one calls it a **superficial inflammation** (Fig. 151). If the exudate can gain free ac-

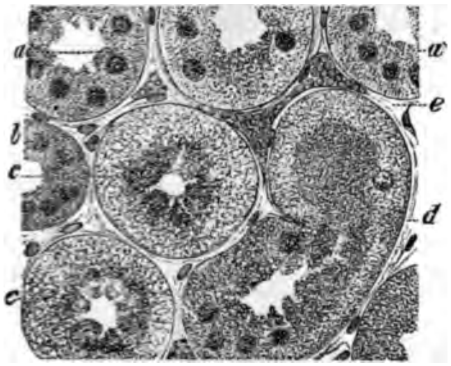


Fig. 150.—Parenchymatous nephritis, with necrosis of the epithelium of the uriniferous tubules, in icterus gravis. *a*, Normal convoluted tubule; *b*, Ascending loop; *c*, Convoluted tubule with necrotic epithelium; *d*, Convoluted tubule with epithelium partly intact, partly necrotic; *e*, Stroma with blood-vessels. (Preparation hardened in Müller's fluid, stained with gentian violet, and mounted in Canada balsam. Magnified 300 diameters.)

cess to the surface, and flows from it mixed with particles of cast-off tissue (Fig. 151, *d*, *e*, *f*, f_1, *h*), the inflammation is called a **catarrh.** If the pouring out of a liquid exudate on the surface of the skin or of a mucous membrane is impeded by coherent, horny epithelium (Fig. 148, *a*), and there form under this cover circumscribed collections of fluid, in which the deep soft layers of epithelium dissolve (Fig. 148, *d*, *f*, *g*), the lesions thus formed are called **vesicles** and **blisters.** When the exudate from serous surfaces collects in the cavities of the body, there are formed in them **inflammatory effusions,** which not rarely reach a considerable bulk, distend the affected cavity, and compress the organs contained therein.

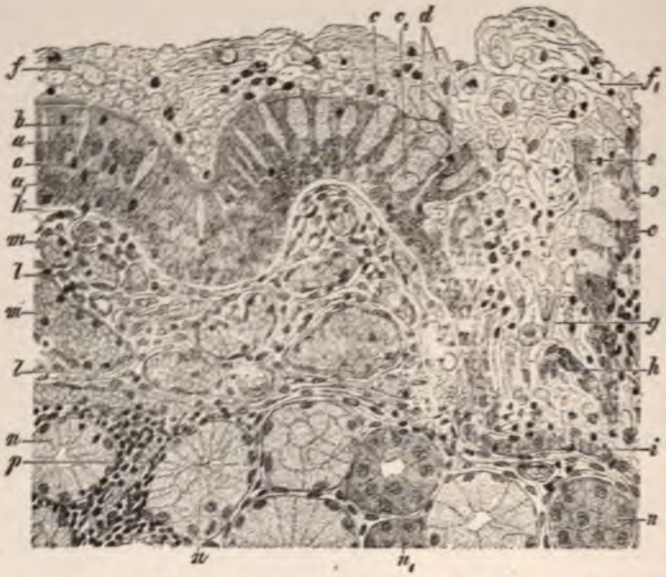


FIG. 151.—Superficial catarrhal inflammation of a bronchus. *a*, Ciliated cells; a_1, Deep cell-layers; *b*, Goblet-cells; *c*, Markedly mucoid cells; c_1, Mucoid cells with mucoid nucleus; *d*, Desquamated mucoid cells; *e*, Desquamated ciliated cells; *f*, Layer of drops of mucus; f_1, Layer of stringy mucus and pus-corpuscles; *g*, Excretory duct of a mucous gland filled with mucus and cells; *h*, Desquamated epithelium of the excretory duct; *i*, Intact epithelium of the excretory duct; *k*, Swollen hyaline basement membrane; *l*, Connective tissue of the mucosa, partly infiltrated with cells; *m*, Dilated blood-vessel; *n*, Mucous gland filled with mucus; n_1, Lobule of a mucous gland without mucus; *o*, Migrating cell in the epithelium; *p*, Cellular infiltration of the connective tissue of the mucous glands. (Preparation hardened in Müller's fluid and alcohol, stained with aniline brown, and mounted in Canada balsam. Magnified 120 diameters.)

If an organ is in a condition of inflammation, it is customary to express it by adding the termination "itis" to the Greek name of the organ. In this way are formed, for example, the terms endocarditis, myocarditis, pericarditis, pleuritis, peritonitis, encephalitis, pharyngitis, keratitis, orchitis, oöphoritis, colpitis, metritis, hepatitis, nephritis, amygdalitis, glossitis, gastritis. The ending "itis" is sometimes affixed to the Latin names. One says, e.g., conjunctivitis, tonsillitis, and vaginitis. If one wishes to denote that the serous covering or the neighborhood of an organ is inflamed, one places before the Greek name with the termination "itis" a "peri" or "para." Thus are formed the words perimetritis, parametritis, periproctitis, perityphlitis, paranephritis, perihepatitis.

For isolated forms of inflammation there are also in use special names; thus one calls inflammation of the lungs, pneumonia; inflammation of the arch of the palate and tonsils, angina.

Since Cohnheim taught us to recognize the migration of colorless blood-corpuscles *en masse* as an important part of inflammation, and showed that they might serve as a new source of origin for the cells present in the exudate, the question of the origin of the cells present in the exudate of fresh inflammations has been many times the subject of discussion. While some regarded all cells present in the exudate as extravasated leucocytes, others believed that the leucocytes coming from the blood formed only an accidental component of the exudate, and that the cells contained in it for the most part have originated on the spot from the tissue "irritated" by the cause of the inflammation.

Stricker is of the opinion that the swelling and hardening of the tissue in inflammation are not caused by the collection of exudate, but by a swelling of the cell-reticulum which traverses the tissues, and that it is a phenomenon of growth of the cells and their prolongations characterized by swelling. The cellular exudate—i.e., the pus—he accounts for partly by a segmentation and division of the cellular reticulum swollen from the inflammation, partly by a transformation of the connective-tissue fibrils into pus-corpuscles. Heitzmann considers the inflammatory tissue-changes as a reversion of the tissues to the embryonal condition, and believes that the living material is not contained in the cells only, but infiltrates the entire ground substance, and increases, in the progress of an inflammation, with the liquefaction of the ground substance. Connective tissue, cartilage, and bone become resolved in inflammation into those elements from which they are formed—i.e., into cells—which then immediately reproduce their like. Grawitz believes that both the cellular infiltrate and the pus occur without any participation of the leucocytes worth mentioning. Everywhere in the tissues cells which he calls slumber-cells lie latent in large quantities, not affected by our nuclei-staining dyes and therefore not recognizable (only from 5 to 10 per cent. of the tissue-cells, according to him, are known to us), but which in inflammation awake, increase in size, respond to nuclei-staining dyes, and therefore again become recognizable.

After what an unprejudiced careful examination of inflamed tissue exhibits, there can be no doubt that the description of the origin of the inflammatory infiltrate given by Stricker, Heitzmann, Grawitz, and their pupils, does not correspond to the conditions as they actually exist.

The cells that accumulate in the tissues in acute inflammations in the first hours and days are leucocytes derived from the blood, and this is true especially of all cells which bear the character of polynuclear and mononuclear leucocytes. A tissue-growth occurs, it is true, almost always in the course of inflammation, but it is able to produce a large quantity of cells only in the course of several days (cf. § 101), *and these cells do not possess the characters of lymphocytes.*

A doubt about the origin of the cells exists only in regard to a part of the mononuclear forms, because proliferating tissue can produce cells which appear very like the larger forms of mononuclear leucocytes and have not yet been certainly distinguished from them.

§ 98. Both the local tissue-degeneration and the exudation may appear very differently in different cases, and one can distinguish conformably different **forms of inflammation.**

If the exudate consists principally of fluid, while the cellular components are comparatively insignificant, it is called a **serous exudate.** If this is within a tissue—for example, the cutaneous and subcutaneous tissues or the kidneys (Fig. 152, *a*)—it leads to **inflammatory œdema.**

Escape of fluid on the surface of a mucous or serous membrane gives the picture of a **serous catarrh**; localized collection of fluid beneath the horny layer of the epidermis, with the liquefaction of the soft layers of epithelium, leads to the formation of **vesicles** and **blisters** with clear contents (Fig. 148, *d*, *f*).

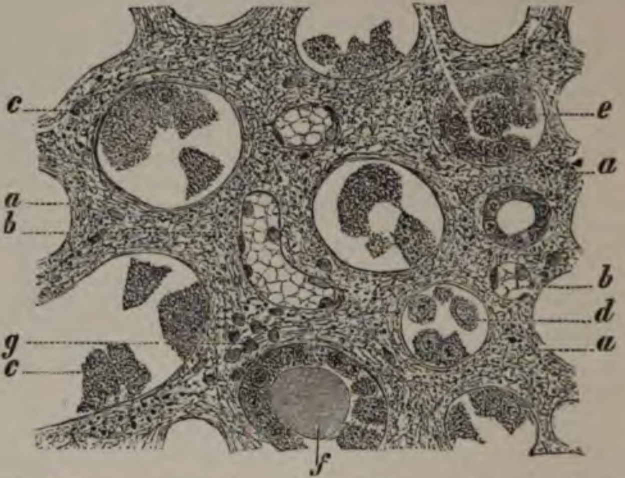


FIG. 152.—Inflammatory œdema of the kidney, with catarrh of the uriniferous tubules (from a man who died of suppurative mediastinitis and pleuritis with nephritis on the tenth day after the beginning of the illness). *a*, Stroma distended by fluid, and infiltrated with granules and filaments of fibrin and separate fat-droplets; *b*, Capillaries; *c*, Epithelia of the convoluted tubules, in parts slightly fatty and desquamating; *d*, Desquamated epithelial cells in a looped tubule; *e*, Granular and fatty detritus in a looped tubule, whose epithelium remains, but is cloudy; *f*, Hyaline cylinder (cast) in a convoluted tubule; *g*, Round cells. (Glycerin preparation treated with osmic acid. Magnified 350 diameters.)

If the fluid exuded on the surface of a mucous membrane is associated with marked mucoid change of the superficial epithelium (Fig. 151, *b*, *c*, c_1) and of the mucous glands (*n*), there is a **mucous catarrh** (Fig. 151, *d*, *f*, f_1). If a marked desquamation of the epithelium of the mucous membrane, with or without mucoid change, occurs, there is a **desquamative catarrh,** and it may occur not only in mucous membranes, but also in the respiratory parenchyma of the lungs, on serous surfaces, in the kidney-tubules (Fig. 152, *c*, *d*), etc.

In desquamative catarrh, if the secretion is mixed with much epithelium, it is cloudy and contains a large number of cells, which consist, according to the source of the catarrh, sometimes of mucoid cylindrical and ciliated cells (Fig. 153, *3*, *6*), sometimes of squamous epithelium (*11*, *12*, *18*, *19*). At the same time there generally are found also round cells (Fig. 153, *1*, *2*, *7*, *9*, *10*, *13*, *20*), and often also bacteria (*4*, *14*, *15*, *16*, *17*, *21*).

If the deposition of fibrin, or coagulation, occurs in a liquid exudate, there are formed **fibrinous and sero-fibrinous exudates,** which are often also called *croupous*. They occur chiefly on the surface of serous or mucous membranes and in the lungs, but masses of fibrin can also be deposited within tissues infiltrated with exudate (Fig. 152, *a*, and Fig. 156, *l*), as well as in lymphatic vessels (Fig. 156, *h*).

Fibrinous exudates on *mucous surfaces* form whitish patches and coherent membranes, which sometimes lie upon them only loosely, sometimes are firmly attached to the under surface. In the serous cavities the deposits of fibrin float in the form of flakes in the fluid exudate, or attach themselves firmly to the surface of the membranes. These deposits consist at times only of small, attached granules and flakes, which give to the affected surface a cloudy, dull, rough, or even granular appearance; at other times they consist of larger yellowish or yellowish-red tough membranes, which often give the surface a felted or villous appearance (cor villosum, pericarditis villosa). In the lung croupous inflammation leads to the filling of the alveoli with a coagulated mass, as a result of which the lung acquires a firm consistency.

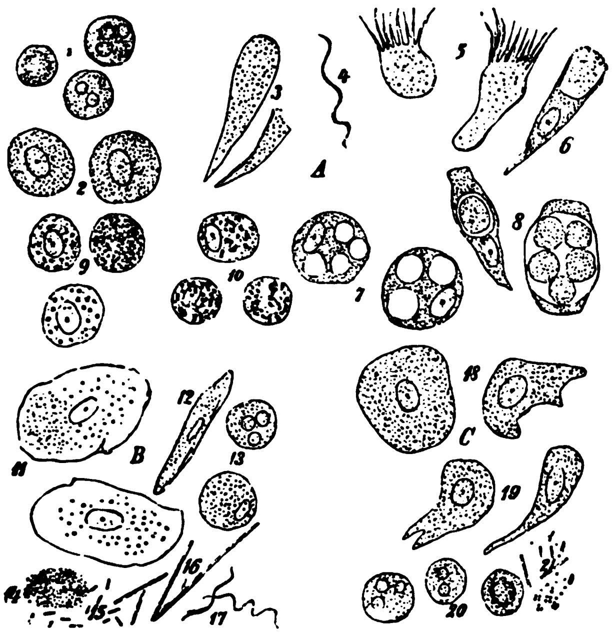


FIG. 153.—Catarrhal secretion of various mucous membranes. A, Secretion from mucous membranes with cylindrical epithelium; B, From the mouth; C, From the urinary bladder. 1, Round cells (pus-corpuscles); 2, Large round cells with bright nuclei from the nose; 3, Mucoid cylindrical cells from the nose; 4, Spirillum from the nose; 5, Mucoid cells with cilia from the nose; 6, Goblet-cell from the trachea; 7, Round cells with mucoid masses from the nose; 8, Epithelial cells containing pus-corpuscles from the nose; 9, Fatty cells in chronic catarrh of the larynx and pharynx; 10, Cells from sputum containing coal-pigment; 11 and 12, Squamous epithelium from the mouth; 13, Mucus-corpuscles; 14, Micrococci; 15, Bacteria; 16, *Leptothrix buccalis;* 17, *Spirochaete denticola;* 18, Superficial; 19, Middle layer of bladder epithelium; 20, Pus-corpuscles; 21, Schizomycetes. (Magnified 400 diameters.)

The formation of croupous membrane on mucous surfaces occurs only if the epithelium is already desquamated and the connective tissue, in part at least, exposed; but tissue covered with epithelium may be coated over with coagulated fibrin extending from spots free from epithelium. The desquamation of epithelium follows, in such a case, sometimes gradually, sometimes quickly, through the lifting up of whole layers of epithelium (Fig. 154, *b*), which are either still well preserved or already degenerated or necrotic (Fig. 163, *b*) and infiltrated with exudate (Fig. 156, *a*).

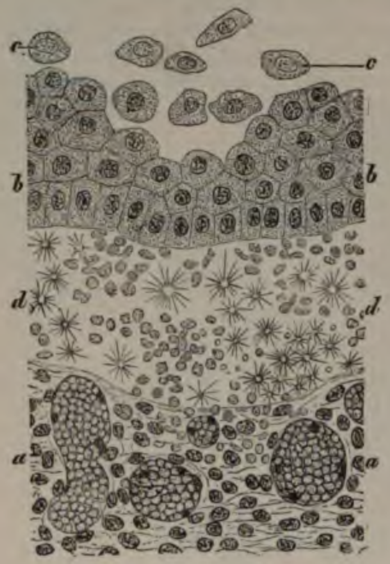
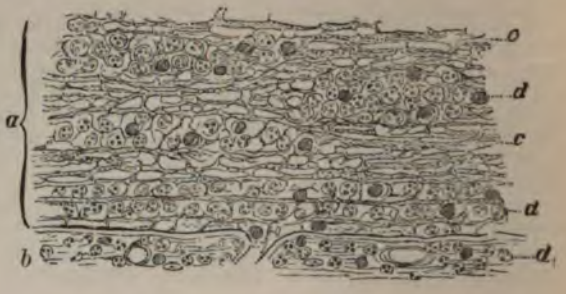


FIG. 154.—Acute hæmorrhagic fibrinous inflammation of the trachea, caused by the vapor of ammonia. *a*, Superficial connective-tissue layer of the mucosa, with widely dilated vessels filled with blood and escaped red blood-corpuscles; *b*, Deep layer of epithelium raised up entire; *c*, Desquamated epithelial cells; *d*, Hæmorrhagic fibrinous exudate with radiating, crystal-like deposit of fibrin partly consisting of small colorless masses. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 300 diameters.)

The deposit of fibrin may begin under the raised-up epithelium, with the formation of slender forms like acicular crystals (Fig. 154, *d*), which are arranged radially about a centre, in which there often lies a small corpuscle, probably a product of disintegration of a red blood-corpuscle, or a blood-plate. There form, however, very soon, thicker or thinner threads (Fig. 155, *c*, and Fig. 156, *b*, *c*) which inclose more or less leucocytes and red blood-corpuscles. The arrangement of the threads is generally reticular, but the thickness of the meshwork and the width of the meshes vary greatly. When there is unequal development of the threads and strands of fibrin, the principal strands have a direction sometimes parallel to the mucous membrane (Fig. 151, *a*), sometimes perpendicular to it (Fig. 156, *c*). Thick fibrin membranes often show a real stratification (Fig. 156, *a*, *b*, *c*), a hint that their formation occurred in batches.

FIG. 155.—Croupous membrane from the trachea. *a*, Section through the membrane; *b*, Upper layer of the mucous membrane, infiltrated with pus-corpuscles, *d*; *c*, Threads and granules of fibrin; *d*, Pus-corpuscles. (Magnified 250 diameters.)



On the *serous membranes* the fibrinous deposits generally present a granular appearance (Fig. 157, *b*); they are composed of finer and coarser threads of fibrin, and inclose sometimes only a few, sometimes many, leucocytes and red blood-corpuscles.

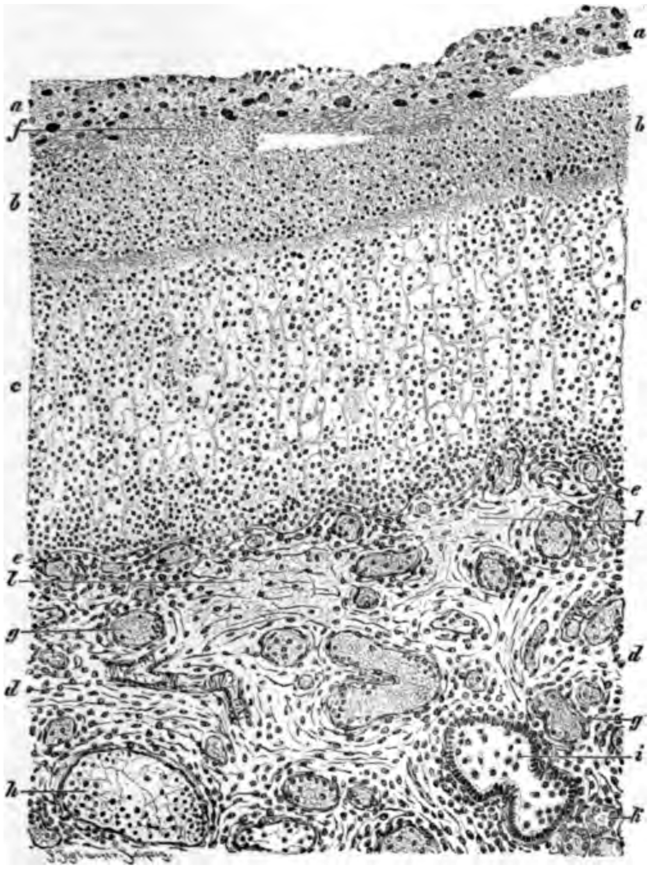


FIG. 156.—Section of a uvula inflamed and covered with a stratified fibrin membrane, from a case of diphtheritic croup of the pharyngeal organs. *a*, Superficial layer of coagulation, consisting of epithelial plates and fibrin and dotted with numerous balls of cocci; *b*, Second layer of coagulation, which consists of a close-meshed reticulum of fibrin inclosing leucocytes; *c*, Third layer of coagulation, lying on the connective tissue, and consisting of a wide-meshed reticulum of fibrin inclosing leucocytes; *d*, Connective tissue infiltrated with cells; *e*, Infiltrated boundary-layer of the connective tissue of the mucous membrane; *f*, Mass of red blood-corpuscles; *g*, Congested blood-vessels; *h*, Lymphatic vessel distended with fluid, fibrin, and leucocytes; *i*, Excretory duct of a mucous gland distended with secretion; *k*, Transverse section of a gland; *l*, Reticulum of fibrin in the superficial layers of connective tissue. (Preparation hardened in Müller's fluid, embedded in celloidin, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 50 diameters.)

In the *lungs* the fibrin generally forms an irregularly arranged reticulum (Fig. 158) composed of very fine or coarser filaments, and inclosing leucocytes, red blood-corpuscles, and desquamated epithelium. In the first stages of fibrin-formation there are also sometimes found filaments which are arranged like a necklace and consist of rows of corpuscles. According to the researches of Hauser, the first deposit of the fibrin reticulum may start from the dead epithelial cells of the alveoli, whose thin plates are infiltrated at the same time with a delicate reticulum of fibrin.

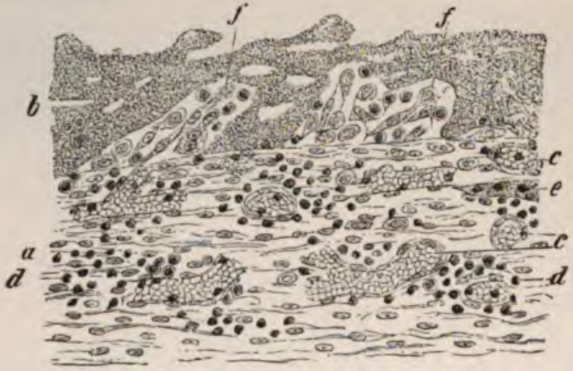


FIG. 157.—Adhesive pericarditis. Section through the epicardium, *a*, and the fibrin membrane, *b*; *c*, Dilated and congested blood-vessels; *d*, Round cells which infiltrate the tissue; *e*, Lymphatic vessel filled with cells and coagula; *f*, Formative cells within the deposit. (Preparation hardened in Müller's fluid and stained with hæmatoxylin. Magnified 150 diameters.)

In the kidneys deposits of fibrin may occur in the form of fine filaments or fibrinous masses in the uriniferous tubules and in the glomerular capsule. In the lymphatic glands fibrin filaments form principally within the lymph-passages.

Hæmorrhagic exudate—i.e., exudate which contains red blood-corpuscles in large quantities—occurs particularly in connection with the deposit of fibrin (Fig. 154, *d*, and Fig. 158). Thus croupous pulmonary exudate always contains a larger or smaller number of red blood-corpuscles, and in the same way, in fibrinous pericarditis and pleuritis, large quantities of red blood-corpuscles quite often escape. Hæmorrhagic inflammations occur also not rarely in the central nervous system, in the lymphatic glands, in the skin, and in the kidneys.

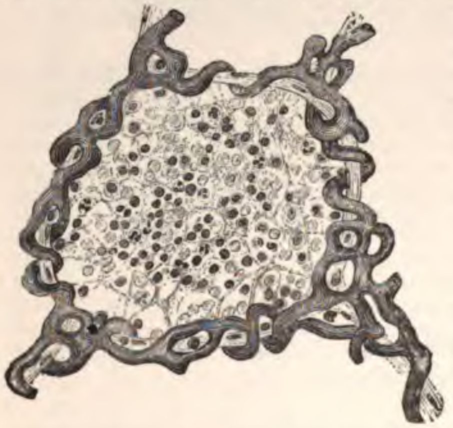


FIG. 158.—Croupous hepatization of lung. Alveolus filled with an exudate consisting of fluid, red and colorless blood-corpuscles, and epithelial cells. (Preparation first injected and then stained with hæmatoxylin. Magnified 80 diameters.)

The serous, fibrinous, and sero-fibrinous inflammations may be caused both by thermic and chemical influences and by bacteria, but are most often the result of infection, especially of infection with the *Diplococcus* *pneumoniæ* and the *Bacillus diphtheriæ.* The former causes particularly croupous inflammations of the lungs and the pleuræ, the latter fibrinous inflammations of the pharynx, palate, and respiratory passages.

Hauser recently emphasizes that the fibrin-formation extends from cells—e.g., from pulmonary epithelia or leucocytes—which are at the centre of the deposit of fibrin. So far as I have observed, this actually occurs; still I have generally seen, in the centre of radiating rods of fibrin, only bright forms without nuclei, which, as I believe, originate not from leucocytes or tissue-cells, but from red blood-corpuscles, and are probably partly identical with the forms described as blood-plates.

§ 99. When the inflammatory exudate consists principally of leucocytes, there is an **infiltration of the tissues with small cells** (Fig. 159, *d, e, f*), which may at times be so crowded as to obscure the structure of the tissue. If leucocytes with fluid exudate appear in large quantities on the surface of a mucous membrane or an external wound, a white fluid is seen on the affected part, which is called **pus**, and has given occasion

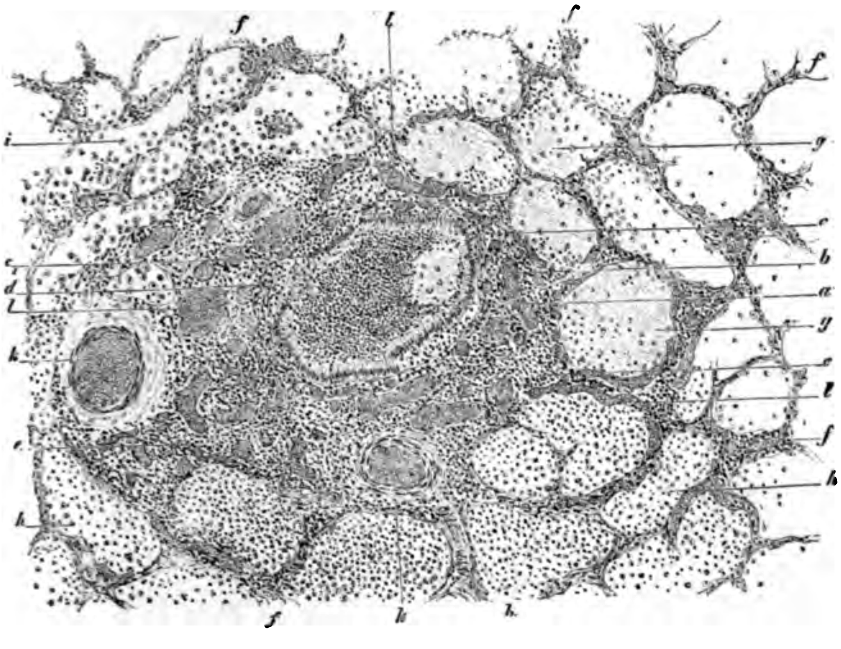


FIG. 159.—Purulent bronchitis, peribronchitis, and peribronchial bronchopneumonia (from a child aged fifteen months). *a*, Purulent bronchial contents; *b*, Mucoid bronchial contents: *c*, c_1, Bronchial epithelium infiltrated with round cells and partly raised up, (c_2); *d*, Bronchial wall infiltrated with cells and its blood-vessels markedly distended with blood; *e*, Peribronchial and periarterial connective tissue infiltrated with cells; *f*, Septa between the pulmonary alveoli, partly infiltrated with cells; *g*, Fibrinous exudate in the alveoli; *h*, Alveoli filled with exudate containing many cells; *i*, Alveoli filled with exudate containing few cells; *k*, Transverse section of pulmonary artery; *l*, Congested bronchial, peribronchial, and interlobular vessels. (Preparation hardened in Müller's fluid, embedded in celloidin, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 45 diameters.)

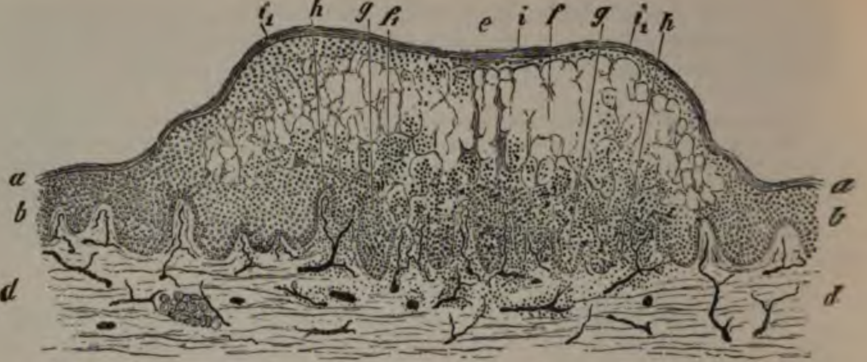


FIG. 160.—Section of a smallpox pustule. *a*, Horny layer; *b*, Mucous layer of epidermis; *d*, Cutis; *e*, Smallpox pustule; *f*, Cavity of the pock, containing at f_1 pus-corpuscles; *g*, Remains of epithelium between the papillæ, infiltrated with pus-corpuscles; *h*, Papillæ infiltrated with cells; *i*, Umbilication with thin pock-cover; i_1, Border of the pock, whose roof is here formed of the horny and transition layers. (Injected hæmatoxylin preparation. Magnified 25 diameters.)

to name the inflammation a **purulent catarrh** (Fig. 159, *a*). When an abundant secretion persists, the phenomenon is called a *blennorrhœa*. If such pus collects within body-cavities—e.g., in the pericardium or in the pleura or in joint-cavities—it forms confined *purulent effusions* or **empye-**

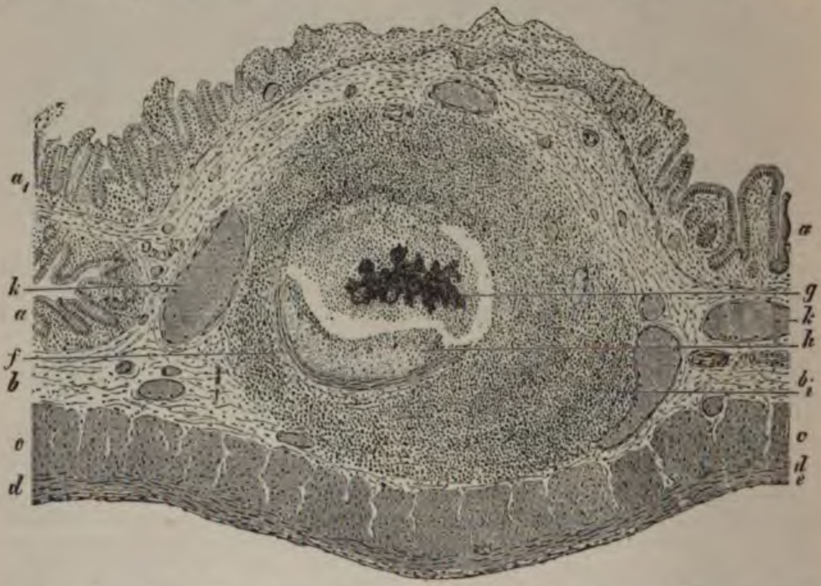


FIG. 161.—Embolic abscess of the intestinal wall, with embolic suppurative arteritis and embolic aneurism, in cross-section. *a, b, c, d, e*, Layers of intestinal wall; *f*, Remains of the arterial wall, in transverse section; *g*, Embolus, surrounded by pus-corpuscles within the dilated and partly suppurating artery; *h*, Parietal thrombus; *i*, Periarterial purulent inflammation of the submucosa; *k*, Vein filled with blood. (Preparation hardened in alcohol, stained with fuchsin, and embedded in Canada balsam. Magnified 30 diameters.)

mata. If an abundant collection of lymphocytes takes place within a blister produced by the liquefaction of epithelium under the horny layer, the fluid becomes more and more turbid, white, purulent, and the vesicle changes to a **pustule** (Fig. 160, f_1).

The cells that emigrate, especially in purulent inflammations, and which are therefore called **pus-corpuscles,** are polynuclear leucocytes. They may reach the surface of a mucous membrane both after the desquamation of the epithelium and while the epithelium is still preserved, and they accomplish this by passing between the epithelial cells (Fig. 159, c, c_1, c_2); and the epithelium of the external skin may be penetrated by them in the same way (Fig. 160, *g*).

When very numerous pus-corpuscles collect in a tissue, so that the tissue acquires a white or grayish-white or yellowish-white color, the process takes on the character of a **purulent infiltration.** If finally liquefaction and dissolution of the tissues take place, we may speak of these changes as **suppuration of tissue** and **abscess-formation** (Fig. 161)—i.e., the formation of a cavity filled with pus.

When the suppurative infiltration and tissue-solution occur on the surface of an organ—for example, of a mucous membrane (Fig. 162, *d*, *f*, *g*)—the process leads to the formation of a superficial loss of substance —an **ulcer.** If there form, through suppuration, pervious cavities, they are called **fistulous tracts.**

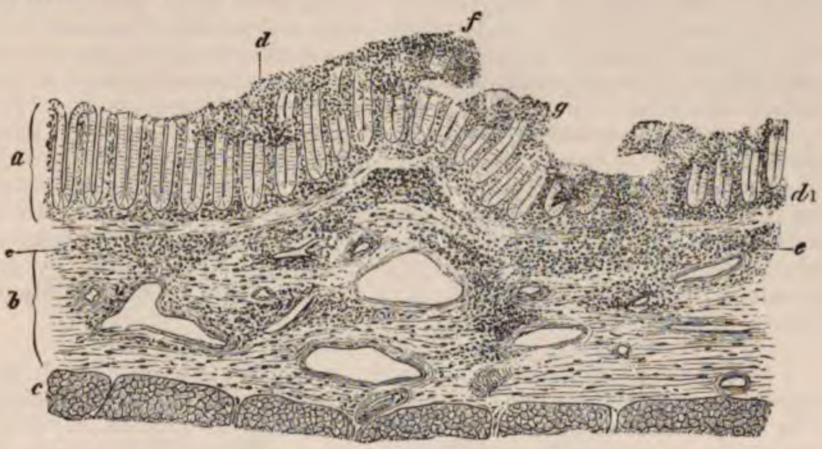


Fig. 162.—Suppuration and necrosis of the mucous membrane of the large intestine in dysentery. Section of the mucosa, *a*, and submucosa, *b*, of the colon; *c*, Muscularis; *d*, Interglandular, d_1, Subglandular infiltration of the mucosa; *e*, Infiltrated area in the submucosa; *f*, Infiltrated upper glandular layer, desquamating; *g*, Ulcer whose base is infiltrated with cells. (Stained with hæmatoxylin. Magnified 25 diameters.)

The dissolution of the tissues, which is designated as suppuration, is only possible on condition that they die. This tissue-necrosis is generally present even before the occurrence of suppuration, and is produced by the specific action of the producer of inflammation. The tissue may, however, die only during the course of the inflammatory infiltration and then liquefy.

If an accumulation of pus-corpuscles is associated with an abundant collection of fluid, there occur **sero-purulent exudates**, which, infiltrating the tissues, give rise to a condition which is often called **purulent œdema.** When a purulent or a sero-purulent inflammation spreads rapidly over wide areas—for example, over a large portion of the subcutaneous or any submucous tissue—the process is called **phlegmon.** It leads often to the formation of extensive pus-cavities, in which there lie shreds of breaking-down tissue infiltrated with pus.

The association of serous exudation and deposition of fibrin with suppuration leads to the formation of **fibrino-purulent exudates**; and both effusions into the body-cavities and meningeal exudates, as well as croupous exudates on mucous membranes and in the lungs, and also phlegmons may bear this character; yet it is to be noted that with increase of suppuration the formation of fibrin decreases and the masses of coagulated material present dissolve. The masses of fibrin infiltrated with pus present a white appearance and are readily friable.

The suppurations and the associated formations of abscesses and ulcers are generally caused by **bacteria**, and most frequently by the *Staphylococcus pyogenes aureus*, the *Streptococcus pyogenes*, and the *gonococcus* (gonorrhœal virus). Yet suppurations are not rare which are caused by *actinomycetes*, or by the *Bacillus typhi abdominalis*, or the *Diplococcus pneumoniæ*, or the *Bacterium coli commune*. Staphylococci generally cause localized inflammations; streptococci, on the other hand, phlegmonous. The presence of certain bacteria (*Bacillus phlegmones emphysematosæ*, Fränkel) may cause the formation of **gas** (*gas-phlegmon*). Suppuration is sometimes ectogenous, sometimes lymphogenous or hæmatogenous, and in the last case often bears the characters of a metastatic process (Fig. 161).

Among the **chemical substances** which may lead to suppuration when introduced into the tissues are mercury, oil of turpentine, petroleum, 5–10 per cent. solutions of nitrate of silver, creolin, digitoxin, dilute croton-oil, sterilized cultures of a variety of bacteria, in which latter the bacterial proteins are the active agents. The suppurations produced by chemical substances differ from the infections by healing more readily, by not spreading in the tissues, nor forming metastases, and by their products lacking virulence when inoculated.

§ 100. As was explained in § 99, suppurative inflammation always leads to tissue-necrosis; but this necrosis is again immediately lost sight of in the presence of the liquefaction and dissolution of the tissues, which form the characteristic feature of suppuration. When the action on the tissues is of a different sort, it may lead to a tissue-necrosis of larger extent, visible to the eye, which is not followed by suppuration, but which rather is characterized by the fact that the necrotic pieces of tissue remain unchanged for a time, and only relatively late are separated by sequestration and desquamation, or are gotten rid of by absorption. As the tissue-necrosis here forms the chief feature, one may fittingly call the disease a **necrotic inflammation.**

The tissue-necrosis associated with inflammation may also be caused by caustic **chemicals** and **high or low temperatures**, and by **ischæmia,** and also by **infection**; and there are special *bacteria* (bacilli of typhoid, diphtheria, and dysentery) which cause tissue-necrosis.

Caustic chemicals produce necrosis chiefly on those tissues with which they first come in contact; but many substances (sublimate, the salts of chromic acid, cantharidin) may only exert a necrotic effect after their diffusion throughout the body by the blood and tissue-juices; this effect showing itself especially in the kidneys, the ducts leading from them, and the intestine, where they are excreted. Bacteria produce necrosis at the spots where they multiply and where the poisonous substances formed by them are collected in a concentrated condition.

The necrosis of the tissue may appear immediately, as the first effect of the injurious action, while the inflammatory exudation only takes place later, and is confined to the region adjoining the necrosis; and this occurs especially after the action of caustic substances, after exposure to a high temperature, and in ischæmia. In other cases, which belong chiefly to the infections, an inflammation is first established, and then afterward necrosis affects the inflamed and infiltrated tissue. In tubercular infections the necrosis appears only after the tissue-proliferation has developed and has existed for some time.

Necrotic inflammations are most often observed on the mucous membranes, and are here generally called **diphtheritic**, particularly those which are caused by infection. The necrosis may here affect at first the epithelium only, which, as a result, loses its nuclei (Fig. 163, *b*), and later acquires a flaky appearance. If white opaque patches form on the mucous membrane, as in the pharynx in diphtheria, one may speak of *epithelial or superficial diphtheritis.* Ordinarily the term *diphtheritis* is applied, however, only to tissue-necrosis in which *the inflamed and infiltrated tissue undergoes necrosis* (Fig. 164, *a*) and changes into a lumpy or granular mass without nuclei, or a rather homogeneous mass containing fibrin, in which the structure of the tissue can no longer be recognized.

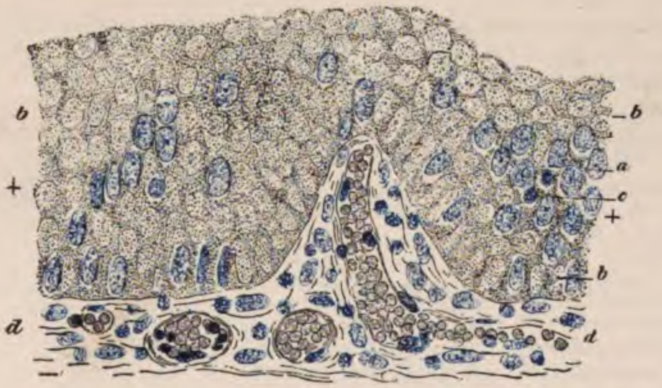


FIG. 163.—Necrosis of the epithelium of the epiglottis. *a*, Living epithelium with well stained nuclei; *b*, Necrotic epithelium with unstained nuclei; *c*, Leucocytes situated in the epithelium; *d*, Hyperæmic, inflamed, and infiltrated connective tissue. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 300 diameters.)

Diphtheritic sloughing of the tissues of a mucous membrane is observed particularly often in the intestine, but is also not lacking in other mucous membranes, as in those of the vagina, the efferent urinary passages, the region of the throat, where the tonsils are oftenest affected, etc. The necrotic tissue forms a slough that is white or grayish white, or, from admixture of blood or bile, or other impurities, is stained dark green, yellow, or brown, or any other color. If a long time has elapsed since its formation, and if there has occurred a tissue-liquefaction on the border separating the dead from the living tissues, the necrosed parts form loosely attached or quite free deposits on the surface of the mucous membrane; these deposits consisting sometimes only of small particles or granules, sometimes of quite large membranes.

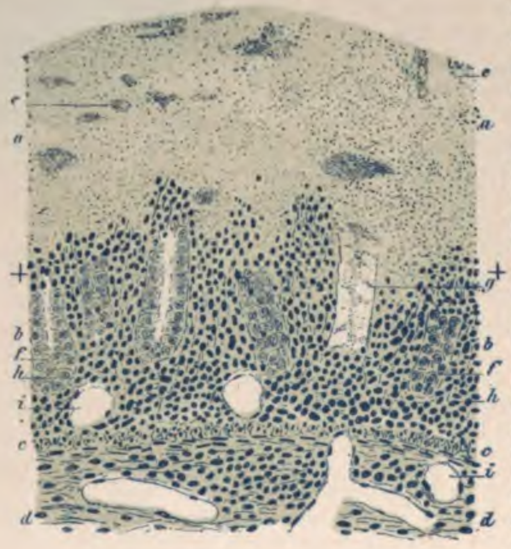
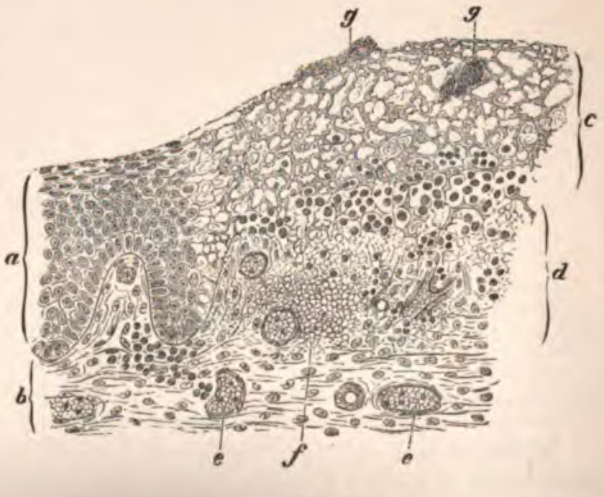


FIG. 164.—Bacillary diphtheritis of the large intestine (dysentery). *a*, Necrotic portion of the glandular layer of the mucosa, infiltrated with bacilli; *b*, Remaining inflamed mucosa; *c*, Muscularis mucosæ; *d*, Submucosa; *e*, Swarms of bacilli; *f*, Glands with epithelium still preserved; *g*, Gland with necrotic epithelium and bacilli; *h*, Connective tissue infiltrated with cells; *i*, Blood-vessels. (Preparation hardened in alcohol, treated with gentian violet, and mounted in Canada balsam. Magnified 80 diameters.)

Diphtheritis of mucous membranes may also be associated with croupous deposits (Fig. 165 *c*, *d*), so that the tissue-necrosis (*d*) may be covered with fibrin excretion (*c*).

FIG. 165.—Section of the uvula in pharyngeal diphtheria with croupous deposits. *a*, Normal epithelium; *b*, Connective tissue of the mucous membrane; *c*, Reticulated fibrin; *d*, Connective tissue of the mucosa, infiltrated with coagulated fibrin and round cells, and partly necrotic; *e*, Blood-vessels; *f*, Hæmorrhage; *g*, Masses of micrococci. (Preparation stained with aniline brown and mounted in Canada balsam. Magnified 75 diameters.)



Wound-granulations may also necrose in the same way as do inflamed mucous membranes, so that one may also speak of *wound-diphtheria*.

Acute tissue-necroses caused by infection are observed in the internal organs—chiefly in the lymphatic glands, the spleen, and the bone-marrow—and are characterized by the formation of partly opaque grayish-white or yellowish-white or dirty-gray sloughs.

In the necrosis caused by tuberculosis the destruction of the tissue occurs only gradually and bears the character of a **caseation.**

When an inflammatory focus contains bacteria, which excite a putrid decomposition of the albuminoid bodies, the inflammation may also bear a **gangrenous, foul-smelling character,** the tissue then decomposing into a dirty-gray or black tinder-like mass, which gradually dissolves and exhales an extremely disagreeable odor. Gas-bubbles are also sometimes developed in the focus.

II. The Processes of Repair Associated with Inflammation.—Formation of Granulation and Cicatricial Tissues.—Absorption of Exudates and Tissue-Necroses, and Substitution of Connective Tissue for Them.

§ 101. When an inflammation—that is, a tissue-degeneration associated with formation of exudate—exists in any tissue, there always arise, earlier or later, processes whose object is to remove the changes established and to restore the degenerated tissue, and which must therefore be regarded as **processes of repair.** If the cause which has excited the inflammation is no longer present, these processes consist really in this: that the pathological exudation ceases and is replaced by a normal vascular secretion; that the exudate present and the necrosed tissue are absorbed or cast out; and that the tissue destroyed is restored. If the excitant of the inflammation is still present and active in the tissue, this must also be excreted or rendered inert.

The **cessation of the alteration of the vascular walls** is attained by supplying normal blood to the injured vessels, so that their nutrition again becomes normal. If the alteration was slight, and if the excitant of inflammation acted only for a short time—if it is the case, for example, only of the brief action of a trauma or high temperature or a chemical substance that was quickly removed—restoration of the vessels may also result in a short time—i.e., in a time that may be measured in minutes and hours.

When the excitant of inflammation acts for a considerable length of time, as in the case of bacteria which remain and multiply in the tissues for some time, or if changes are established by the inflammation itself which act in such a manner as to alter the vessels—if there has been, for example, a tissue-necrosis—the vessels continue for quite a long time to experience an injury which hinders the complete restoration of their functions.

The **absorption of the exudates** occurs in many cases easily and quickly, because it is taken up by the lymphatic circulation. It occurs most quickly in serous exudates; yet in many places fibrinous exudates also may be quite rapidly removed, but only when the coagula soon liquefy. Firm fibrinous exudates, as they occur especially on serous surfaces, and also large collections of pus, generally offer considerable resistance to absorption, and are the cause of the prolonged duration of the inflammation, although the character of this may change from what it was at first.

In very many cases absorption is accomplished by the simultaneous substitution for the exudate of embryonic tissue, which is converted later into connective tissue.

The **sequestration and absorption of necrosed tissue**, with the exception of the casting loose of dead epithelium, which may be very quickly accomplished, always requires a long time, which, however, varies very considerably with the nature, situation, and extent of the dead tissue. The inflammation generally lasts as long as necrotic tissue is still present. *Superficial necrosed tissues may be cast off after the separation of the dead from the living*—i.e., *after sequestration*. In deep-seated tissue-necroses, in which the tissue does not soon undergo total liquefaction, absorption is generally slow, and is performed by a gradual substitution of living tissue for the dead.

The **regeneration of degenerated tissue** is dependent, for its occurrence, partly on the degree and extent of the degeneration, partly on the nature of the tissue, partly on the mode of action of the excitant of the inflammation.

When the tissue-cells in the neighborhood of the inflammation are only slightly degenerated, they can soon be restored when the nutrition is normal. When single cells have been destroyed, but the organization of the whole is not damaged, in most tissues a rapid renewal of cells by regenerative growth of the remaining cells may occur. This is the case particularly in the various connective-tissue formations, the superficial epithelium, the liver, and the kidneys; while ganglion-cells, bone-cells, cartilage-cells, and heart-muscle cells possess either no power, or at most a very slight power, of regeneration (cf. Section V.). Extensive tissue-destructions with solutions of continuity, wounds, fractures, suppurations, necrosing inflammations, etc., lead to tissue-developments, which are indeed competent to repair the defect, but which lead generally not to a restoration of the normal tissue, but to the formation of a deteriorated tissue, that is called in its young condition **granulation tissue**, in its complete development **cicatricial tissue.** Of the same character is also the tissue which is substituted in the course of time for the exudates that are not readily absorbed, and for the tissue-necroses.

With the occurrence of regenerative growth and granulation, a new phenomenon appears in the course of inflammation, and gives to the inflammation, later on, a special character, so that one calls it a **proliferating inflammation.**

The **phenomena of proliferation** begin in inflamed tissue, at the earliest, after eight hours, but are generally first clearly recognizable after twenty-four or forty-eight hours have elapsed.

They occur in general the more quickly the milder the inflammation is and the faster the pathological exudation is subdued or diminished. Suppuration, necrosis, and gangrene of the tissue hinder its proliferation, and retard the beginning of repair proportionately, or at least confine the reparative processes to the neighboring tissues.

Every tissue capable of growth furnishes formative cells only for tissue like or closely allied to it. Pus-corpuscles are not formed from the tissue-cells, but cells newly developed from the tissue-cells by proliferation may become mixed with the exudate, degenerate in it, and die. Thus not all cells newly developed by proliferation can fulfil their function of producing new tissue.

The **removal of the excitant of inflammation** takes place very differently in different cases, and depends in the first place on the nature of the excitant. Many traumatisms and thermic influences act for only a very short time, and have no further influence on the later course of the inflammation. Many substances which act chemically may be quickly taken up by the tissue-juices and made inert or excreted, while others remain locally active a longer time. Of the bacteria which produce inflammation, many die soon, while others remain and constantly form new generations, which also continually renew inflammation; generally, it is true, in such a way that in the first diseased focus the inflammation subsides and healing begins, while in the neighborhood, or even in distant regions, metastatic inflammations develop.

On account of the great variation which exists both in the nature and the qualities of the excitants of inflammation, as well as in the course of the inflammatory tissue-degenerations and of the exudate, and in the course of the processes of repair, it is easy to comprehend that the whole progress of an inflammation to the final healing may be of a very different character in different cases, so that all the different possibilities of its course can hardly be reviewed. At the same time it is not difficult to comprehend the decline of the various forms of inflammation, because ultimately the entire process is always made up of similar processes—i.e., of tissue-degenerations and pathological exudates that form the essence of inflammation, and of processes of repair that are appropriate for there moval of the disturbances established by the inflammation.

Many authors consider the tissue-proliferations which arise during the course of inflammation as also constituting an essential part of inflammation. For example, Neumann groups under the term inflammation all those phenomena which develop locally after a primary tissue-lesion and are directed to the healing of this lesion. If this be so, regeneration forms the most important part of the inflammatory process, for it is preëminently fitted to restore the defect of tissue caused by the primary tissue-lesion, or, as Neumann says, the uninterrupted continuity of the tissues. Such an identification of inflammation with tissue-regeneration I hold as inadmissible, in the first place because tissue-regenerations occur which clinically and anatomically in no way bear the characters of an inflammatory process. Then also the inflammatory pathological exudates cannot be regarded as a phenomenon that can be compared to regeneration, and that, like it, has for an end the healing of a primary tissue-lesion. Even if they may act benignly in individual cases, yet this is not always the case. They cause much more often serious damages, which increase those established by the primary tissue-lesion, and often enough they form hindrances to the early beginning of healing.

In my opinion, all processes of healing, including also tissue-proliferation, should be separated from inflammation, as not pertinent to the essential nature of inflammation. At the same time one may properly speak of *inflammatory tissue-growth* or of *proliferating inflammation*, for by these terms are understood tissue-growths which are connected with inflammation and run their course simultaneously with progressing inflammatory exudation, or inflammations during whose course regenerative tissue-growths have already developed.

§ 102. The **granulation tissue** which forms in the course of numerous inflammatory processes exhibits nothing else than an **embryonic tissue** formed by cell-proliferation and **infiltrated with leucocytes.** Primarily the tissue consists actually of *cells and newly formed vessels*, which at first depend for their support upon the ground substance of the tissue from which they develop, but soon form for themselves a new ground substance.

The **cells of granulation tissue** are partly **hypertrophied tissue-cells** (Fig. 166, *b*, *c*, *d*), partly **mono-** and **polynuclear leucocytes** (Fig. 166, *a*, a_1). In most cases the hypertrophied cells are connective-tissue cells, which later on produce connective tissue (Fig. 166, *d*, *e*), and may therefore be termed **fibroblasts**. Granulation tissue, however, may contain the offspring of other tissues, e.g., of periosteal tissue, medullary tissue, muscle-tissue—or *osteoblasts*, *chondroblasts*, and *sarcoblasts*—which are able to form bone-, cartilage-, and muscle-tissue. There may also be found: in or upon the granulation tissue, within newly formed glands, *glandular epithelial cells;* in mucous membranes and the integument, *covering epithelial cells;* and these are able forthwith to form epithelial-tissue structures. The formative cells of granulation tissue may move away from the places of their origin, and are thus in a certain sense *wandering cells*. In the formation of connective tissue they take on the most varied forms (Fig. 166, *c*, *d*, *e*). Sometimes polynuclear cells also form (c_1). They are distinguished by their large, bright, oval nuclei, which, being less deeply stained by nuclei-staining dyes, are thus distinguished from the nuclei of leucocytes, which are very deeply stained. The formative cells of connective tissue are often termed *epithelioid cells* on account of their resemblance to epithelial cells.

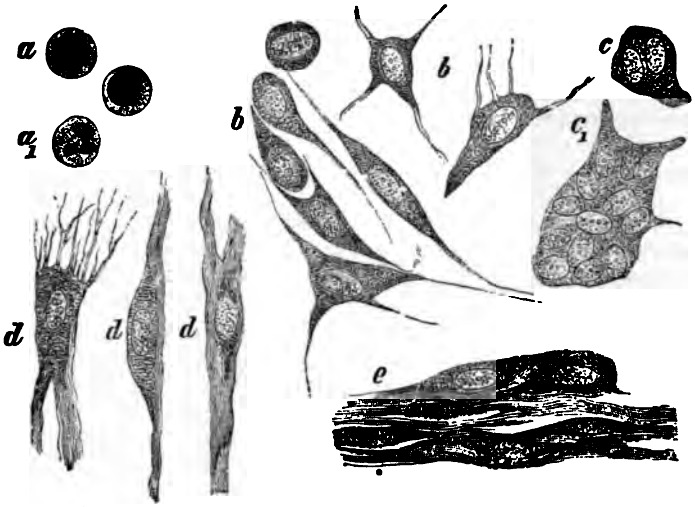


FIG. 166.—Isolated cells from a wound-granulation. *a*, Mononuclear leucocytes; a_1, Polynuclear leucocytes; *b*, Various forms of mononuclear formative cells; *c*, Binuclear formative cells; c_1, Polynuclear formative cells; *d*, Formative cells in the stage of connective-tissue formation; *e*, Completed connective tissue. (Stained with picrocarmine. Magnified 500 diameters.)

The **leucocytes of granulation tissue** are cells that have migrated from the blood-vessels, and from their presence it may be concluded that the inflammatory exudation from the vessels still continues. Their number may also be regarded in general as an index of the degree of the still existing inflammation, which complicates the recovery.

The **blood-vessels of granulation tissue** develop by sprouting from old vessels (cf. Fig. 132), and permit one very soon—indeed, at the time when an emigration of leucocytes occurs (Fig. 167, *b*)—to recognize processes of proliferation (*a*); and in the formation of granulation tissue they take on a very lively growth. The young embryonic tissue is in consequence supplied with unusually abundant vessels, which make it appear red. At the time of the change of the granulation tissue into connective tissue or **cicatricial tissue** an *obliteration of the vessels* occurs, and with it a blanching of the cicatrix.

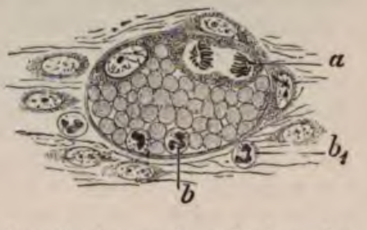


FIG. 167.—Blood-vessel from the deep layer of the skin cut transversely, forty hours after painting the skin of a rabbit with tincture of iodine. *a*, Endothelial cells with mitoses; *b*, b^1, Leucocytes. (Preparation fixed in Flemming's acid-mixture and stained with safranine and picric acid. Magnified 350 diameters.)

§ 103. If an **open wound** occurs on any part of the surface of the body, and if it is not infected by bacteria or seriously injured in any other way, its walls and base after twenty-four hours appear deeply reddened and somewhat swollen. One can still clearly recognize the individual components of the tissue, only the tissue appears somewhat infiltrated, and here and there one sees small shreds of necrotic tissue. On the second day the gelatinous condition of the tissues is more apparent. The limits of the individual tissue-elements are confused, the color grayish red. On the wound lies a reddish-yellow fluid. After the second day there appear over the whole wound small red papules, which rapidly increase in number and size, become confluent, and after two or three days form a granular red surface—a **granulation surface.** This is covered with more or less abundant wound-secretion, that forms a gray, gelatinous layer, later a more yellow, creamy one. The latter consists of a coagulable exudate rich in albumin; and numerous round cells, that usually have two or three round nuclei, are termed *pus-corpuscles*, and, being incapable of further development, undergo destruction.

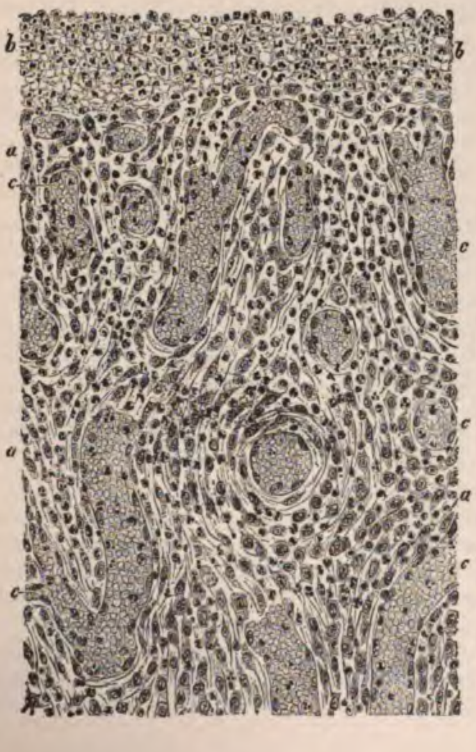


FIG. 168.—Wound-granulations from an open wound, with fibrinopurulent surface deposit. *a*, Granulation tissue; *b*, Fibrino-purulent layer; *c*, Blood-vessels. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 150 diameters.)

The changes which the surface of the wound shows are caused in the first two days by local hyperaemia and infiltration of the tissue with cellular and fluid exudate, and by the imbibition and liquefaction of the tissue. After that there is joined thereto a tissue-growth and new formation of vessels which lead to the formation of **wound-granulations.** After a few days there will be found to have developed in the wound an embryonic tissue [illegible] (Fig. [illegible]) [illegible] consisting of fibroblasts [illegible] leucocytes [illegible]. The leucocytes which generally belong to the polynuclear form are found in all layers of fresh granulation, but are massed especially in the superficial strata and embedded in fibrin over the granulation surface.

The fibroblasts at first are round cells, but later there develop cells partly rod-shaped, partly spindle-shaped, partly with many branches, which are [illegible] in various ways (Fig. [illegible]). At the same time the number of large formative cells increases so that they finally surpass the small round cells in number and in places lie close together. When their number has reached a certain point the development of connective tissue begins—i.e., the formation of the fibrillary intercellular substance (Fig. [illegible] and Fig. [illegible])—which is performed in the manner described [illegible]. When there is a certain [illegible] of fibrils the formation of [illegible] arrests the process. The remainder of the formative cells [illegible] remain as fixed connective-tissue cells (Fig. [illegible]) [illegible]. The process has then reached [illegible]—[illegible] has become **cicatricial tissue.**

In **open wounds of the integument,** [illegible]

[illegible]

The repair of [illegible] **wounds of the** [illegible]

[illegible]

The [illegible] the surfaces of the wound [illegible] exudate [illegible] material [illegible] blood (**Fig.** [illegible]) [illegible] opposing surfaces of the wound. There also occurs very often an inflammatory infiltration of the edges of the wound, which varies in degree in different cases, and when the course of repair is aseptic, it is never very extensive (*g*, *h*), being greatest about the second, third, or fourth day,

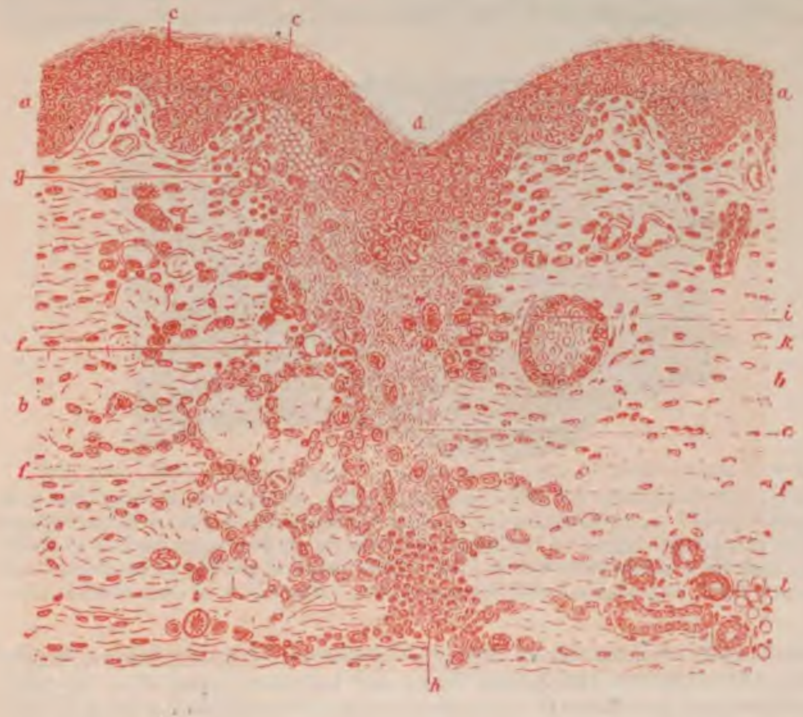


FIG. 169.—Repair of an incised wound of the skin united by suture. Preparation shows condition on the sixth day. *a*, Epidermis; *b*, Corium; *c*, Fibrinous exudate; c_1, Bloody exudate; *d*, Newly formed epidermis, which contains numerous figures of dividing nuclei and has plugs of epithelium driven into the subjacent exudate; *e*, Karyokinetic figures in epithelium remote from the incision; *f*, Growing embryonic tissue, which develops from the connective-tissue spaces and contains cells with karyokinetic figures and some vessels with proliferating walls; *g*, Proliferating embryonic tissue with leucocytes; *h*, Collection of leucocytes in the deepest angle of the wound; *i*, Fibroblasts lying within the exudate, one with a karyokinetic figure; *k*, Sebaceous gland; *l*, Sweat-gland. (Preparation hardened in Flemming's acid-mixture, stained with safranine, and mounted in Canada balsam. Magnified 80 diameters.)

growing less from the fifth to the seventh, and completely disappearing at or soon after the end of the second week. The inflammatory infiltration is generally greater in the neighborhood of the wound-sutures than elsewhere.

As early as on the second day, regenerative proliferative processes begin in the connective tissue and vessels, and lead, in the course of several days, to the formation of an embryonal tissue, which is situated partly in the spaces of the connective tissue at the edges of the wound (Fig. 169, *f*), partly in the open space of the wound itself (*i*); and here the new tissue gradually grows into the coagulation-mass which is present, and replaces it. In different parts of the wound this tissue is usually present in very different quantity (Fig. 169), and may be entirely absent in places. After several days, whose number varies considerably according to the size of the wound, the thickness of the exudate between the edges of the wound, and the intensity of the proliferation, a blending takes place between the masses of embryonal tissue that have developed from the edges of the wound, and later this is followed by a formation of young connective tissue, which joins the edges of the wound together, and at the same time extends into the old tissue, so that the limits between old and new grow more and more dim.

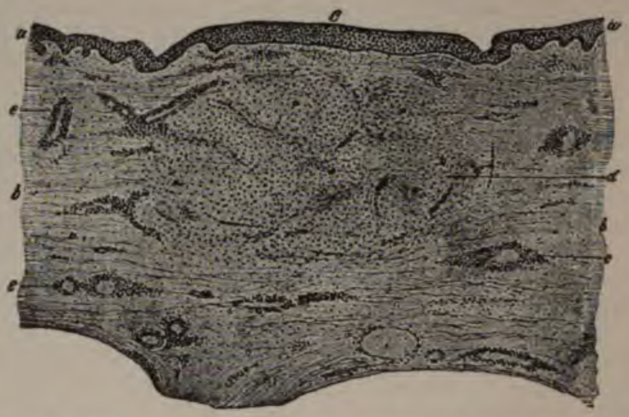


FIG. 170.—Cicatrix of skin remaining after a laparotomy performed six months earlier. *a*, Epithelium; *b*, Corium; *c*, Epithelial surface of the scar; *d*, Dense connective tissue of the scar, rich in cells; *e*, Perivascular foci of leucocytes and large connective-tissue cells. (Preparation hardened in alcohol and Müller's fluid, and stained with hæmatoxylin. Magnified 16 diameters.)

While connective tissue is being newly formed in the depth, the epithelial covering on the surface is also regenerated (Fig. 169, *d*) by the occurrence, here and there in the epithelial covering of the edges of the wound, of a division of the epithelial cells (*d*, *e*). As a result of this the epithelium gradually pushes across the exudate in the wound-opening, covers over the young embryonal tissue, and after a time again forms a horny layer.

The young connective tissue of the cicatrix that unites the edges of the wound is distinguishable for a long time by its richness in cells (Fig. 170, *d*), as well as by the finer fibrillation of its ground substance from the surrounding old cutaneous tissue. In large incised wounds of the skin (Fig. 170) one can find here and there, after the lapse of weeks, or even months, slight appearances of proliferation and inflammation (*e*). In general, however, transformation processes develop gradually in the blanching scar, and as a result this new tissue approaches closer and closer to the normal, until finally the place of the incision can no longer be recognized (Fig. 170). When, however, the wound heals by the interposition of abundant embryonal tissue, a lack of the papillæ may persist (Fig. 170, *c*), so that the region of the wound remains smooth.

§ 104. When an **adherent layer of fibrin** (*b*) occurs on the surface of an inflamed serous membrane (Fig. 171, *a*), **granulation formations** generally develop very quickly underneath it. Their first beginnings can be observed as early as on the fourth day after the formation of the fibrinous deposit, and they consist at first of the appearance of *fibroblasts* (*f*) in the deepest layers of the fibrin membrane. The fibroblasts result from a proliferation of the tissue-cells of the affected membrane, these cells having wandered, later on, to the surface and penetrated into the crevices of the fibrin. There is soon added to these phenomena a new formation of blood-vessels, and in the course of days or weeks there develops on the surface a vascular embryonal tissue or granulation tissue (Fig. 172, *b*, *d*), which gradually replaces the fibrin, but often incloses remnants of fibrin (*c*) weeks later.

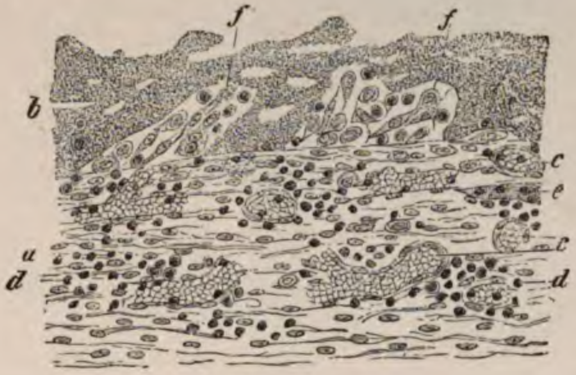


FIG. 171.—Fibrin-deposit and beginning formation of granulations in a fibrinous pericarditis five days old. *a*, Epicardium; *b*, Fibrinous membrane; *c*, Dilated, congested blood-vessel; *d*, Round cells infiltrating the tissue; *e*, Lymphatic vessel filled with cells and coagula; *f*, Formative cells within the deposit. (Preparation hardened in Müller's fluid and stained with hæmatoxylin. Magnified 150 diameters.)

The final result of the process is the formation of **connective tissue,** which causes either only a *thickening* of the fibrin-covered serosa, or an *adhesion of opposing surfaces of the serous membrane*, so that the *inflammation is termed adhesive.*

The result in individual cases depends partly on the abundance of the fibrinous deposit, partly on the situation of the affected organ and its condition during the process of recovery.

Small deposits of fibrin, limited to one surface of the serous membrane, lead only to thickening of the membrane, which, growing pale with the disappearance of the vessels, presents a white thickening that is very often called a *milk-patch* or a *tendinous spot.* Firm gluing together of two serous laminæ by an abundant deposit of fibrin may also lead to their becoming united by abundantly developed connective tissue. With a smaller quantity of fibrin, and repeated rubbing past one another of the membranes, there are generally formed only loose membranous or filamentous adhesions, which still permit the serous surfaces to slide past one another. Very large quantities of *fibrin* may also, at times, partly resist absorption, so that they persist in the newly formed connective tissue and then generally become *calcified*. *Coagulated exudates in the lung* are generally soon liquefied and *absorbed;* yet their removal in this manner may be associated with *connective-tissue proliferation*, which terminates in *induration of the lung*.

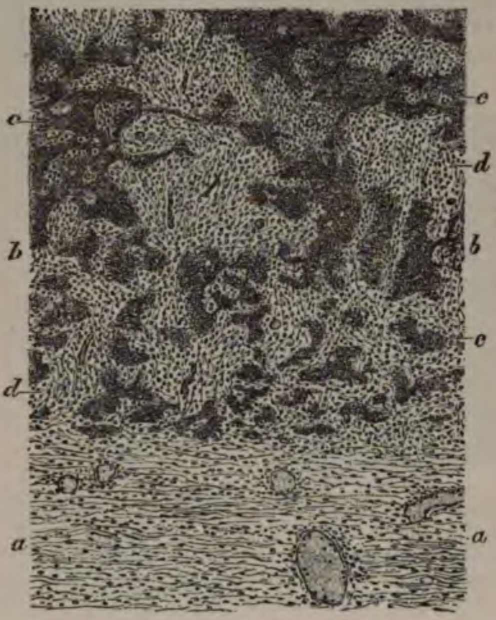


FIG. 172.—Formation of granulations within a fibrinous deposit in pericarditis several weeks old. *a*, Epicardium; *b*, Deposit on the epicardium, consisting of granulation tissue, *d*, and fibrin, *c*. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 45 diameters.)

Masses of coagula within the vessels, which are termed thrombi, give rise, when no infection intervenes, to an inflammatory proliferation of the vessel-walls, a proliferating vasculitis—i.e., a process which is associated with cell-migration, and which exactly corresponds to the inflammatory proliferation of the serous membranes. It is entirely immaterial whether the thrombus has been caused by a preceding inflammatory process or by any other conditions; for the presence of the coagulated mass is itself sufficient to produce inflammation and tissue-proliferation.

The first change which is introduced in the **replacement of the thrombus by connective tissue** is here also the appearance of fibroblasts (Fig. 173, *h*), which arise from the vessel-wall, and later, with the aid of vessels that grow in from the vessel-wall and its neighborhood, form an embryonal tissue that is finally converted into connective tissue. The complete replacement of an obstructing thrombus or embolus results in the obliteration of the lumen of the vessel by vascular connective tissue (Fig. 175, *g*). Replacement of a peripheral thrombus, on the other hand, results in fibrous thickening of the wall. Owing to incomplete replacement and liquefaction of the part not replaced, there arise strings and threads of connective tissue, which cross the lumen of the vessel. Calcification of the parts of thrombi which are not replaced by connective tissue leads to the formation of vascular calculi.

Necrotic tissues, which cannot be sequestrated and discharged externally, are also **replaced by vascular connective tissue** that becomes changed into **cicatricial tissue**; and this replacement is accomplished in the same way as in the case of the fibrinous exudates and thrombi. A preliminary condition for this replacement is that the necrotic tissue shall contain no substances (bacteria) which hinder a tissue-proliferation and produce severe inflammation. For the rest, it is immaterial how the necrosis has occurred, and whether the necrotic tissue is free

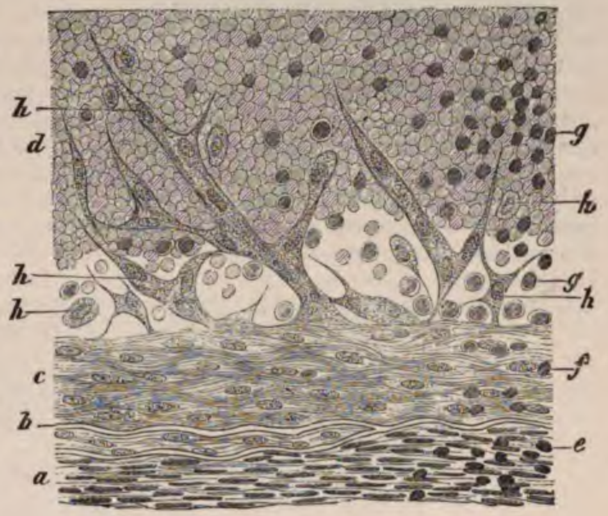


FIG. 173.—Development of embryonal tissue in a thrombosed femoral artery of an old man, three weeks after ligation. *a*, Media; *b*, Elastic boundary-layer; *c*, Intima thickened by old chronic inflammatory processes; *d*, Coagulated blood; *e*, Cellular infiltration of the media; *f*, The same of the intima; *g*, Round cells, partly within the thrombus, partly between the latter and the intima; *h*, Different forms of formative cells. (Preparation hardened in alcohol, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 300 diameters.)

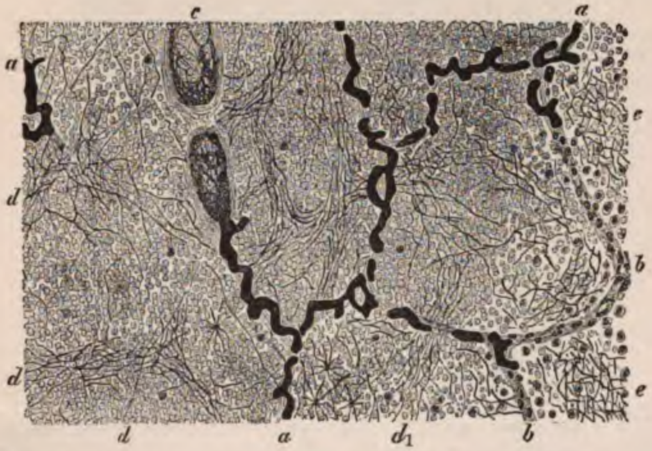


FIG. 174.—Border of a recent hæmorrhagic infarct of the lung. *a*, Non-nucleated alveolar septa, whose capillaries are filled with hyaline thrombi; *b*, Nucleated septa; *c*, Vessels filled with red thrombi; *d*, d_1, Alveoli filled with coagulated blood; *e*, Fibrino-cellular exudate in the alveoli. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 100 diameters.)

from exudate or is infiltrated with exudate or blood (Fig. 174, *d*, d_1). Under these conditions the first phenomenon leading to healing is the following: the inflammatory infiltration (*e*) in the neighborhood of the necrosis becomes associated with a tissue-proliferation, which produces **granulation tissue**, and this in turn grows toward the necrosis (Fig. 175, *d*, *e*), pushes it aside, and replaces it. If this process is not disturbed by any influence, even extensive tissue-necroses may disappear in the course of weeks or months, and be replaced by connective tissue. It may also happen, however, that certain tissues resist absorption (e.g., bone; cf. Fig. 181), or that the development of granulations stops so early that *the remainder of the necrosis persists and then becomes calcified.*

When, owing to an inflammation or an ischæmia within an organ, only the more sensitive elements die—for example, the epithelia or the muscle-cells—while the connective tissue is preserved, the absorption of the necrosis is performed quickly, and in a short time there develops a

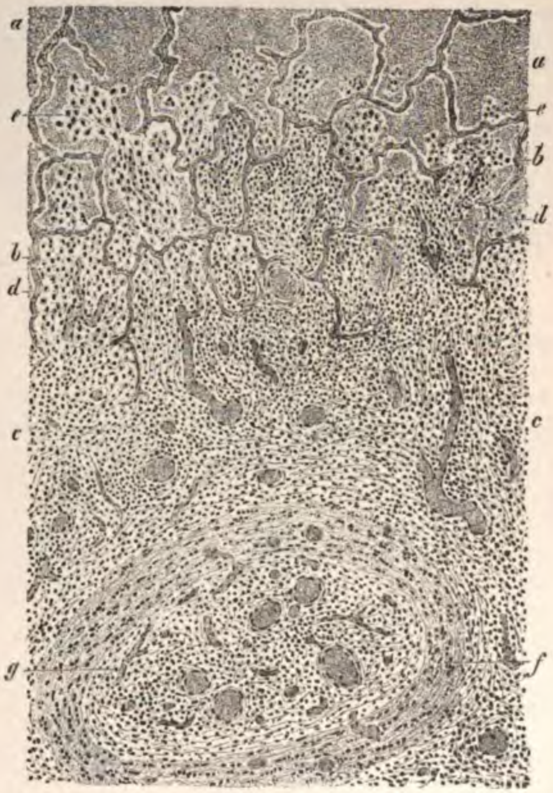


FIG. 175.—Peripheral portion of a healing infarction of the lung. *a*, Blood-extravasation changed into a granular, yellowish mass; *b*, Necrotic alveolar septa without nuclei; *c*, Newly formed connective tissue; *d*, Vascular granulation tissue within the alveoli; *e*, Fibroblasts within alveoli containing the residue of the hæmorrhage; *f*, Artery; *g*, Vascular connective tissue formed within the artery at the place of the embolus. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 45 diameters.)

scar or callus of connective tissue (Fig. 176, *e*), in which the specific tissue-elements are lacking.

Pus is quickly *absorbed* from small abscesses, and *the defect is closed by granulation and scar tissue.* Large amounts of pus may also be absorbed from the cavities of the body and from the lungs.

Abscesses cause a **development of granulations** in their neighborhood, and this leads to the formation of an **abscess membrane.** The cavity may be obliterated by the absorption of the pus and by the growing together of the granulating abscess membrane; and so the abscess may heal, leaving a **scar** behind. Incomplete absorption may lead to thickening of the pus, and later to *calcification of the residue.* If the thickening of the pus, however, does not occur, the abscess remains, and may increase in size in the course of time by secretion from its wall.

Like abscesses, **empyemata** may heal by the absorption of the pus. At the time of absorption the tissues inclosing the pus produce **granulation and cicatricial tissues,** which may attain considerable size when the absorption takes a long time. When incompletely absorbed, *inspissated pus may calcify.*

Foreign bodies, so far as they are capable of absorption and exert no specific influence on their environment, are dissolved and replaced by connective tissue in the same way as are tissue-necroses or masses of fibrin.

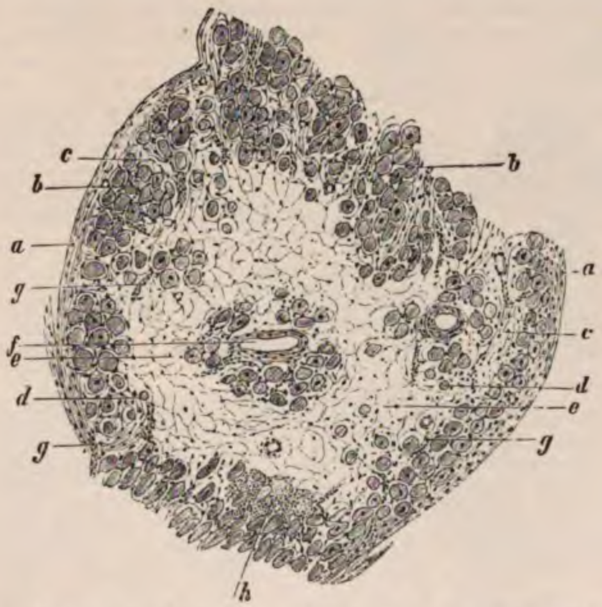


FIG. 176.—Callosity of heart. Section through a muscle trabeculum that has undergone fibroid degeneration. *a*, Endocardium; *b*, Transverse section of normal muscle-cells; *c*, Connective-tissue hyperplasia rich in cells; *d*, Atrophic muscle-cells in hyperplastic connective tissue; *e*, Dense connective tissue without nuclei or muscle-cells; *f*, Veins, in whose neighborhood a few muscle-cells still remain; *g*, Small blood-vessels; *h*, Small-celled infiltration. (Preparation stained with hæmatoxylin. Magnified 40 diameters.)

III. Phagocytosis Occurring in the Course of Inflammations, and the Formation of Giant Cells around Foreign Bodies.—Chemotaxis.

§ 105. When **small foreign bodies,** or **portions or particles of devitalized tissue,** are found in the human body, there is very often a marked *assembling of cells* at their place of deposition. These are, first, *leucocytes* which have migrated from the vessels, but later also *tissue-cells that have become motile, that are proliferating, or that come from an already established centre of proliferation,* wander into the neighborhood of the foreign body or the remains of devitalized tissue.

According to the researches of Leber, Buchner, Massart, Bordet, Gabritschewsky, and others, it is certain that this assembling of cells is partly brought about by **chemotaxis**—i.e., by an attraction exerted by fluid materials derived from the foreign bodies or from the particles of devitalized tissue; but doubtless other conditions also exert an influence in determining the spot where the cells are to assemble.

If the materials, while still undissolved, reach the sphere of the motile cells, they are very often taken up by them, and there occurs that phenomenon which is termed **phagocytosis.** If one observes the process under the microscope—which is easy to do, if tissue-lymph that has been taken from the frog and that is rich in cells, is mixed with granules of soot—one sees that the motile cells pour their protoplasm, if one may use the expression, around the foreign bodies, and absorb them completely into their

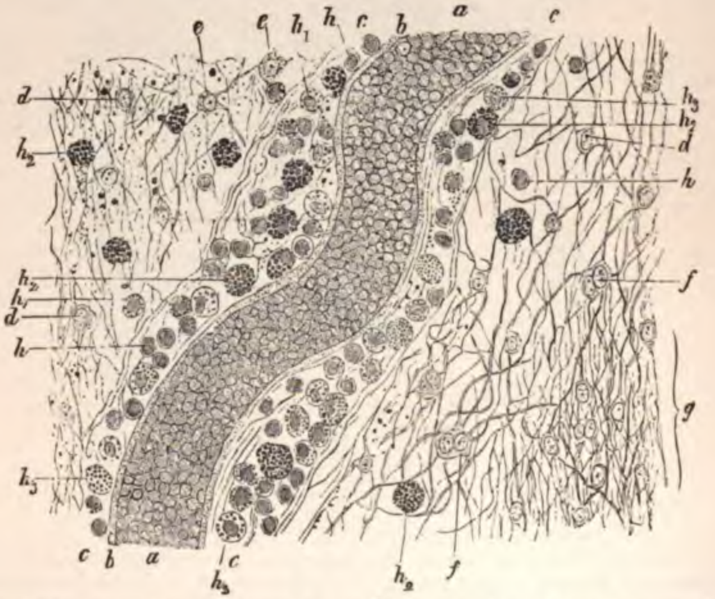


FIG. 177.—Granular cells in a focus of degeneration of the brain. *a*, Blood-vessel with blood; *b*, Media; *c*, Adventitia with lymphatic sheath; *d*, Unchanged glia-cells; *e*, Fatty glia-cells; *f*, Binuclear glia-cells; *g*, Sclerosed tissue; *h*, Round cells; h_1, Round cells with single droplets of fat; h_2, Fatty-granule spheres; h_3, Pigmented-granule spheres. (Teased preparation treated with osmic acid. Magnified 300 diameters.)

protoplasm by the union of the pseudopodia extended over the bodies. Among the foreign bodies that have penetrated from the outside, which are particularly often taken up by the leucocytes or tissue-cells, are chiefly the *various forms of dust* (especially soot), which are taken into the lungs with the respired air, and *bacteria*. It is to be noted, however, that phagocytosis does not occur in all infections caused by bacteria, but is rather confined to special infections, and even in these does not appear in all stages of the local disease.

Among the débris of tissues one finds most often fat-droplets (Fig. 177, h_1, h_2) and products of the destruction of the red blood-corpuscles (Fig. 177, h_3, Fig. 179, *c*, and Fig. 180). These products of destruction may be taken up by the cells until they are stuffed with them and converted into large granular forms that are termed *fatty-granule spheres* and *pigmented-granule spheres*. Besides fat and blood-pigment, other fragments of tissue also—as, for example, particles of the contractile substance of muscle-cells or of elastic tissue-fibres or even of fibrin—may be taken up by the cells. The cells which take up all these substances are principally tissue-cells in luxuriant proliferation—fibroblasts, osteoblasts, sarcoblasts, etc. If an inflammatory exudation runs its course at the same time as the proliferation, and if the proliferating tissue contains *leucocytes*, these *may also be taken up by the phagocytes* (Fig. 178, *a*, *b*, *c*).

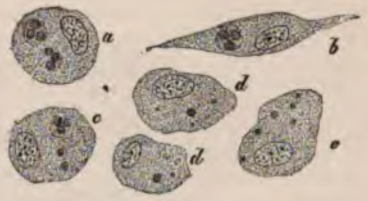


FIG. 178.—Phagocytes from granulating tissue with included leucocytes and their fragments. *a*, Round fibroblast with two leucocytes; *b*, Swollen spindle-shaped connective-tissue cell with one leucocyte; *c*, *d*, *e*, Fibroblasts with fragments of leucocytes. (Preparation hardened in sublimate, stained with Biondi's staining mixture, and mounted in Canada balsam. Magnified 500 diameters.)

The substances taken up by the phagocytes may be partly dissolved and destroyed within the cells; and this is true particularly for the leucocytes, which gradually disappear inside of the cell-protoplasm of the phagocytes (Fig. 178, *c*, *d*, *e*), but it also holds equally for various fragments of tissue, except blood-pigment (Fig. 179, *c*), which may remain a long time within the cells. The insoluble substances (soot) behave in the same way, while the bacteria taken up by the cells, in each case according to

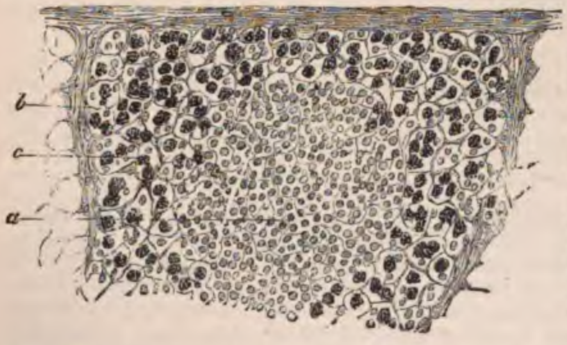


FIG. 179.—Mass of pigmented-granule spheres in a lymphatic gland. *a*, Lymph-node; *b*, Trabeculæ of the lymphatic gland; *c*, Lymph-passage with pigmented-granule spheres. (Preparation hardened in alcohol, stained with carmine, and mounted in Canada balsam. Magnified 80 diameters.)

their vital properties and the condition in which they entered the cells, are sometimes dissolved and destroyed, but sometimes, on the other hand, remain and multiply even in the cells.

The cells loaded with foreign bodies are situated at first at the place where the phagocytosis occurred, but they may also migrate farther and enter the lymphatic circulation (Fig. 179, *c*) and later also the blood, from which they are deposited principally in the spleen, marrow of bone, and liver (cf. §§ 17 and 18).

If the **foreign bodies** which have penetrated into the body from the exterior, or the **dying** or already **necrotic fragments of tissue**, are too numerous to be taken up by leucocytes or proliferated tissue-cells, there form very often, in the granulation tissue that develops in their neighborhood, **polynuclear giant cells**, which arrange themselves on the surface of the foreign body or the superfluous mass of tissue, exactly as this occurs on the part of osteoclasts under physiological conditions (Fig. 180, *d*). If the bodies are not too large they may be still taken up by these polynuclear cells; in the other case the cells remain attached to the surface and produce the gradual dissolution of soluble substances (e.g., strands of catgut, fragments of dead muscle-fibres). It sometimes happens that mononuclear cells take up small foreign bodies into their interior, and after this, by division, their nuclei become polynuclear. This is observed most often after the inclusion of bacteria (lepra, tuberculosis), which still multiply within the cells.

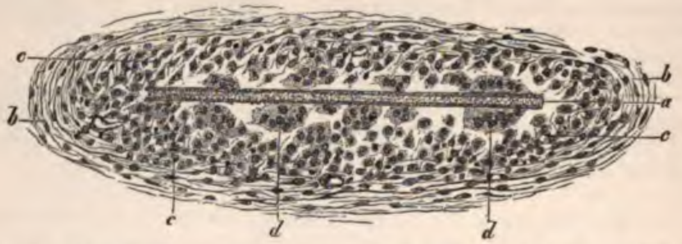


FIG. 180.—Dog's hair encapsulated in subcutaneous tissue. *a*, Hair; *b*, Fibrous tissue; *c*, Proliferating granulation tissue; *d*, Giant cells. (Preparation hardened in alcohol, stained with Bismarck brown, and mounted in Canada balsam. Magnified 66 diameters.)

When a foreign body in the tissues cannot be absorbed it is surrounded by granulation tissue that changes later into connective tissue (Fig.180, *b*, *c*), and in this way becomes encapsulated. The proliferation may be very slight, however, about smooth, completely insoluble substances (glass beads).

The phenomena of **chemotropism** or **chemotaxis**—i.e., the attraction or repulsion of freely motile cells by substances soluble in water—were first observed by Strahl and Pfeffer, who made researches particularly on myxomycetes, infusoria, bacteria, seminal filaments, and swarming spores. Researches of Leber, Buchner, Massart, Bordet, Gabritschewsky, and others have shown that the leucocytes may also be attracted (*positive chemotropism* or *chemotaxis*) or repelled (*negative chemotropism*) by chemical substances. There are particular products of the vital activity of fission-fungi (Leber, Massart. Bordet, Gabritschewsky) or bacterial proteins—i.e., the albuminoid bodies of dead bacterial cells (Buchner) —which even after great dilution (according to Buchner, the protein of pyocyaneus is still active in a dilution of 1 to 3000) are positively chemotactic. According to Buchner, this property belongs also to gluten-casein from wheat-paste and legumin, glue from bones, and alkali albuminate from pease, while ammonium butyrate, trimethylamine, ammonia, leucin, tyrosin, urea, and skatol exhibit negative chemotaxis.

Phagocytosis is a vital phenomenon that has been long known and has many times been made the subject of investigation. Von Recklinghausen, Ponfick, Hoffmann, Langerhans, Slavjansky, von Ins, Ruppert, Langhans, Rindfleisch, and others conducted such experiments in the sixties and seventies, and described particularly the relations of cells to granules of dust and the disintegration products of the blood. In the year 1874 I made the observation that the fibroblasts of the granulation tissue take up and destroy leucocytes. It is to be assumed that one has in this phenomenon *an act of nutrition*—that the phagocytes digest and assimilate the leucocytes taken up. This is indicated by the fact that phagocytosis is a vital function of cells, which in the first place is directed to the taking up of nutriment. But since a phagocytosis is also observed in cells which give off substances to the excreta (e.g., in the renal epithelia); since, also, wandering cells loaded with dust appear at the surface of mucous membranes and in glands, and may thus cleanse the tissues of the substances mentioned, one may regard phagocytosis as a process which is directed also partly to the excretion of certain substances.

Since the year 1883 Metschnikoff has occupied himself in a particularly thorough fashion with phagocytosis (he has also introduced this name), and has demonstrated that it is one of the most widely spread phenomena in the whole animal world, and is most often observed in mesodermal cells. He is of the opinion that phagocytosis represents the essential and characteristic token of inflammation, and that *the inflammatory process is a combat waged by the cells against intruders or disease producers*. This view is, however, completely erroneous and finds no support in the actual conditions. Metschnikoff, in putting forward his definition of inflammation as a battle of phagocytes against disease producers, pays no attention to those phenomena which have been termed inflammation from antiquity onward, and names inflammation only a single chosen vital process to which he has given his interest. If one starts from processes that are recognized on all sides as inflammation, it is apparent that legitimate inflammations occur in which no phagocytosis is present; so that phagocytosis does not even form an inseparable concomitant of inflammation. For the rest, it is to be remarked that phagocytosis is a phenomenon that often occurs in the course of even non-inflammatory processes (e.g., within tumors). Finally, one cannot see in phagocytosis any appearance of a struggle, since in the taking up of cinnabar or soot or fragments of red blood-corpuscles or pus-corpuscles every possibility of resistance on the part of that which is devoured is excluded. And even when bacteria are taken up, no struggle can be observed, at least in those cases in which (as actually often happens) the bacteria are only taken up when they are dead or at least dying. (§ 26 and Section IX. contain more on this subject.)

IV. Chronic Inflammations.

§ 106. Inflammation is naturally an acute process, but various conditions may cause the phenomena of tissue-degeneration and exudation to last longer, and the inflammation to become chronic.

The **cause of an inflammation becoming chronic** may be found, in the first place, in the fact that *in the course of an acute inflammation changes occur which prevent a rapid healing*. As may be deduced from the foregoing, all large defects of tissue and tissue-necroses, as well as large masses of exudate that are difficult to absorb, act in this way. When necrotic masses of tissue are not completely absorbable, as in the case of large pieces of bone, they may indeed be sequestrated, but they then persist as sequestra for years (Fig. 181, *a*), and maintain a constant inflammation.

When a large superficial defect of the integument is produced by a burn, granulations develop, but it may be months before the wounded surface is skinned over from the edges and the process thus completed.

A further cause of chronic inflammations is always found in *repeated injury by external influences.* Thus, for example, repeated inhalation of dust may cause chronic inflammation of the lung; repeated friction of the skin, chronic inflammation of the skin; repeated pathological alterations of the stomach-contents, inflammation of the stomach. In the canals of the body in which *concretions* form, these may also be a cause of lasting tissue-lesions.

When *unfavorable nutritive conditions* exist in a tissue—e.g., great congestion—these may also enable even slight external influences, that under normal conditions produce no inflammation or one that soon stops, to set up ulceration without any tendency to heal. In this way, for example, chronic ulcers of the leg may occur.

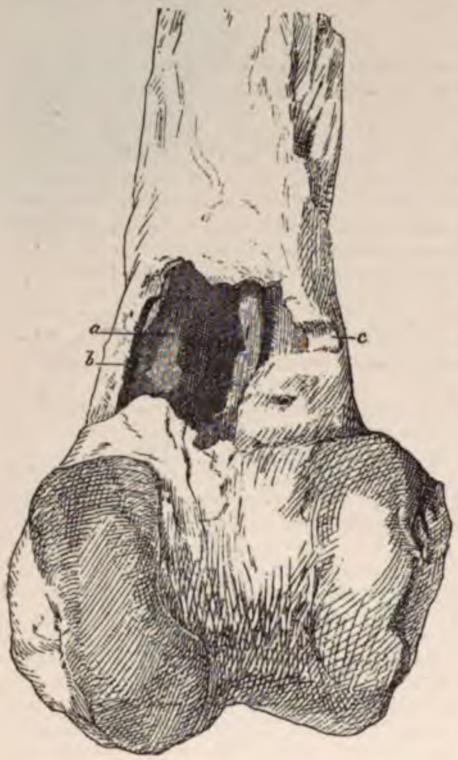


FIG. 181.—Necrosis of fifteen years' duration in the lower part of the diaphysis of the femur. *a,* Sequestrum; *b, c,* Edges of the opening in the thickened bone. (Alcohol preparation. Reduced to two-thirds natural size.)

Infections are also a frequent cause of chronic inflammations, especially those by *bacteria and moulds,* which multiply in the body and so constantly produce new inflammatory irritation. The inflammations which they cause are distinguished from others chiefly by having often a *progressive character,* and by causing metastases by way of the lymphatic vessels and the blood.

Finally, *chronic intoxications* form a last cause. They act particularly on the kidneys and liver, and may be attributed either to the introduction into the organism, through the intestinal canal or the lungs or even the integument, of substances that are injurious to the organs affected or to others; or to the production in the body itself, by disturbances of the processes of metabolism, of injurious substances, so that there is a *chronic auto-intoxication.*

§ 107. The **forms of chronic inflammation** are determined partly by their fundamental causes, partly by the nature of the tissue affected.

The remains of acute processes, as they are seen in fibrinous exudates and tissue-necroses, lead, when not complicated by specific infections, to an **inflammatory tissue-proliferation.** For the rest, **inflammatory hypertrophies of connective tissue** result from various chronic irritations of the tissues. So, for example, chronic irritation of the lung by *the deposition of stone-dust may lead to a connective-tissue hypertrophy in the lung*, which is essentially characterized by the formation of circumscribed nodules (Fig. 182, *a*), but occurs also partly in the form of a diffuse hypertrophy (*c*). Continued irritating conditions in the neighborhood of the orifices of the urogenital apparatus, where they are maintained by the discharge of irritating secretions, often lead to the formation of *acuminate condylomata*—i.e., to hypertrophy of the papillæ, in which the inflamed and infiltrated papillæ, with their vessels, enlarge (Fig. 183, *a*) and often also divide into branches. The epithelium covering the papillæ is also apt to become hypertrophic.

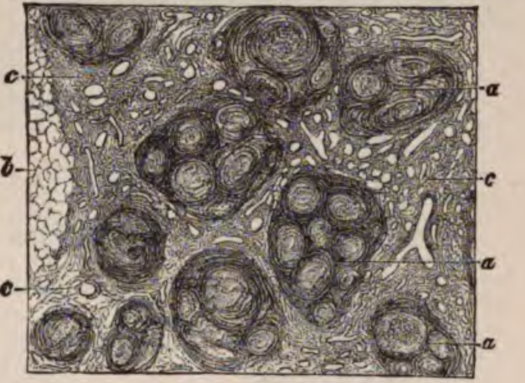


FIG. 182.—Section of a stone-cutter's lung with bronchopneumonic fibrous nodules. *a*, Group of fibrous nodules; *b*, Normal lung-tissue; *c*, Pulmonary tissue, thickened, but still containing bronchi, vessels, and a few alveoli. (Preparation hardened in spirit and stained with picrocarmine. Magnified 9 diameters.)

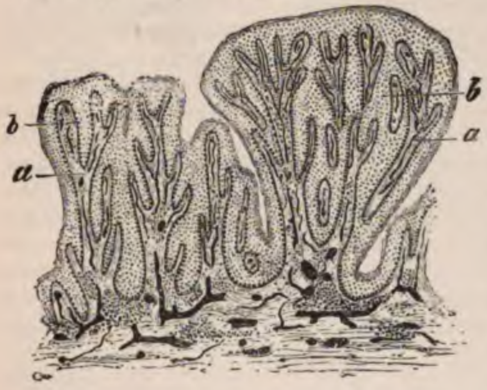


FIG. 183.—Condyloma acuminatum. *a*, Enlarged and branching papillæ; *b*, Epidermis. (Injected preparation, stained with hæmatoxylin. Magnified 20 diameters.)

Repeated continued mild inflammations of the skin and subcutaneous tissue, which are caused by mechanical lesions (scratching), by parasites, or by any other continued irritation, may also often, when they acquire a considerable extent, lead to diffuse connective-tissue hypertrophy, which is known as *elephantiasis*.

Inflammatory growths of the periosteum and medulla of bone, which lead to *pathological new formation of bone*, or a *hyperostosis* (Fig. 184), may be caused both by non-specific irritations—e.g., by inflammations which run their course in the neighborhood of chronic ulcers—and by specific infections, as the syphilitic and tubercular.

Chronic catarrhs of mucous membranes are sometimes caused by specific infections (gonorrhœa, tuberculosis), sometimes by a non-specific injury (concretions, pathological changes in the contents of stomach and intestine), sometimes by continued disturbances of the circulation (congestions).

Chronic abscesses generally result from acute abscesses, and have the same etiology, but may, however, also develop more gradually, and are then caused by special infections, generally tuberculosis or actinomycosis. They are usually limited externally by a connective-tissue membrane covered with granulations, and may increase in size partly by the secretion of pus from the abscess-wall, partly by the destruction of the wall and its neighborhood. Enlargement advancing toward the deep-lying parts leads to the formation of **burrowing or congestive abscesses.** Their growth is really always to be ascribed to the persistence of the infection. Perforation into neighboring tissues leads accordingly, also, to new infectious inflammations.

The tubercular and actinomycotic forms of chronic abscess are distinguished from others partly by the peculiar quality of the pus, partly by a special construction of the abscess membrane (see Tuberculosis and Actinomycosis in Section IX.).

Chronic ulcers are generally caused by specific infections (tuberculosis, syphilis, glanders), but non-specific harmful factors also lead to chronic ulceration in tissue which is specially susceptible to such ulceration. Thus chronic congestions in the vascular system of the leg may interfere with the healing of ulcers caused by any mechanical influence that may have been exerted under the ordinary conditions of the leg. In the same way the peculiar qualities of the stomach-contents may prevent the healing of an ulcer of the stomach. When healing begins at the border of an ulcer, while the ulceration advances at other parts, the ulcer is termed *serpiginous.* Active growth of granulation tissue in an ulcer leads to the formation of an *ulcus elevatum hypertrophicum;* dense, callous, gristly induration of the edge and base leads to the formation of an *ulcus callosum*, or *indolens*, or *atonicum*.

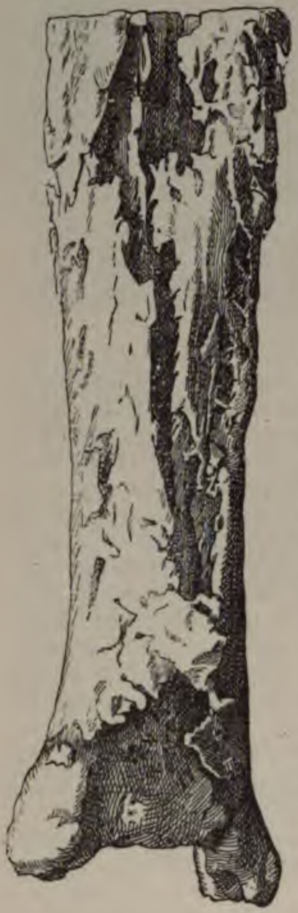


FIG. 184.—Periosteal hyperostosis of the tibia, at the base of a chronic ulcer of the leg. (Reduced to three-fifths natural size.)

Chronic granulation growths (granulations) which persist as such a longer or shorter time, without undergoing conversion into connective tissue, reach, under various **specific infections**, conditions in which they are best known as *tuberculosis, syphilis, leprosy, glanders, rhinoscleroma*, and *actinomycosis*. Since the granulations, in these infections, often produce spongy growths and tumor-like formations, they are also called

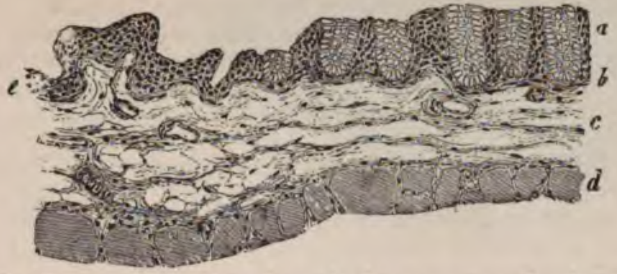


FIG. 185.—Transverse section through the mucosa and submucosa of an atrophic large intestine. *a*, Glandular layer reduced to one half its height; *b*, Muscularis mucosæ; *c*, Submucosa; *d*, Muscularis; *e*, Mucous membrane entirely atrophied. (Magnified 30 diameters.)

fungous granulations or **caro luxurians,** and **infectious granulation tumors** or **granulomata.** They show all the special peculiarities that enable one to recognize, from the structure, the development and life-history of the granulation formations, as well as their special etiology (cf.

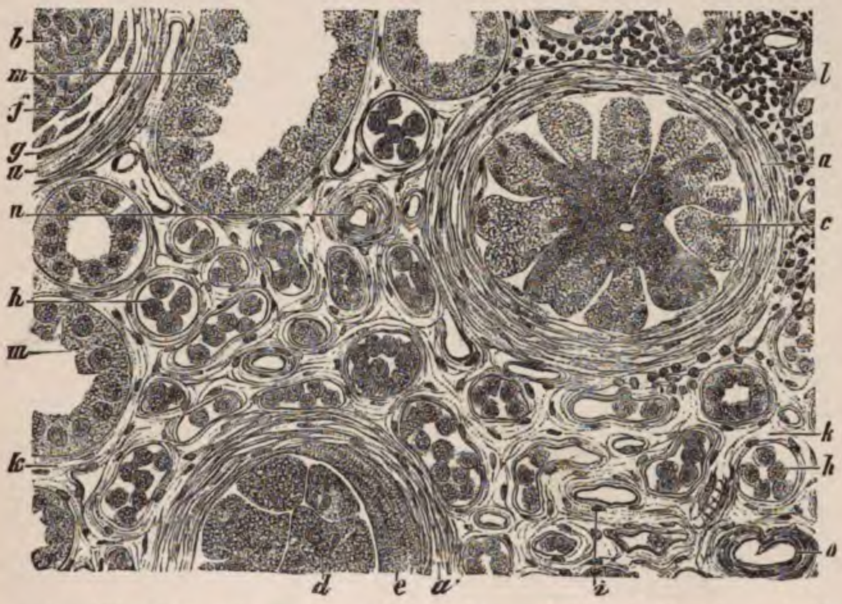


FIG. 186.—Induration and atrophy of the renal tissue in chronic nephritis. *a*, Thickened and fibrous Bowman's capsule; *b*, Normal glomerular vessels; *c*, Glomerulus whose vascular loops are partly impermeable and homogeneous, and its epithelium mostly lost; *d*, Completely ruined glomerulus; *e*, Homogeneous mass of coagulation, studded with nuclei, and consisting of exudate and epithelium; *f*, Desquamated glomerular epithelium; *g*, Epithelium from the capsule; *h*, Collapsed urinary tubule with atrophic epithelium; *i*, Collapsed tubule without epithelium; *k*, Hyperplastic connective-tissue stroma; *l*, Collection of small cells; *m*, Normal, somewhat dilated urinary tubule; *n*, Afferent vessel; *o*, Vein. (Alcohol preparation, stained with alum carmine and mounted in Canada balsam. Magnified 250 diameters.)

Section IX.). It should, however, be mentioned that the etiology of some granulomata that develop in the skin is still unknown.

Chronic inflammations, in which **atrophy of the specific tissue** is associated with **hypertrophy of the connective tissue**, are observed principally in the mucous membrane of the intestinal canal, and in the kidneys and liver.

In the **intestinal canal** the cause may reside both in specific causes (dysentery) and in non-specific irritations, which are set up by any abnormal property of the contents of the intestinal canal. The epithelial constituents either die with continual desquamation, while the connective tissue remains, or they decay at the same time as the connective tissue on which they are situated undergoes necrosis and destruction. The final result is a mucous membrane (Fig. 185) which contains either no glands (*e*) or only rudimentary ones (*a*).

In the **liver** and **kidneys** the chronic inflammations that lead to atrophy and induration, and whose results are called **cirrhosis of the liver** and **indurated contracted kidneys**, are hæmatogenous diseases, so far as they do not depend on disturbances in the domain of the excretory ducts (obstruction, formation of concretions), and are caused partly by *infections*, partly by *intoxications*. They begin either acutely or more insidiously, and are characterized by atrophy and degeneration of the glandular tissue (Fig. 186, *h*, *i*), by hypertrophy of the connective tissue (Fig. 186, *a*, *k*, and Fig. 187, *b*), by cellular infiltration, by the formation of granulations (Fig. 186, *l*, and Fig. 187, *e*), by obliteration of old vessels (Fig. 186, *c*, *d*), and by the formation of new vessels. In the liver there is often also the formation of new bile-ducts (Fig. 187, *d*), which, however, for the greater part do not perform their function.

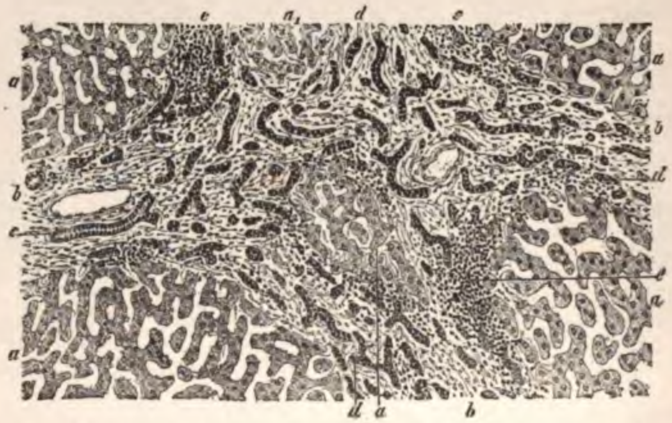


FIG. 187.—Connective-tissue hyperplasia and development of bile-ducts in chronic hepatitis. *a*, a_1, Lobules of the liver; *b*, Hyperplastic periportal connective tissue; *c*, Old bile-ducts; *d*, Newly formed bile-ducts; *e*, Collection of small cells. (Preparation hardened in alcohol and stained with hæmatoxylin. Magnified 60 diameters.)

SECTION VII.

Tumors.

I. General Considerations.

§ 108. A **new growth** or **neoplasm** or **tumor** in the restricted sense is *a new formation of tissue, possessing an atypical structure, not exercising any function of service to the body, and presenting no typical limit of growth.*

Tumors may be found in any tissue possessing capability of growth, and when developed they usually have *borders sharply defined* against the surrounding tissue; still *a whole organ may turn into a tumor*, or *large masses of tissue may take on such characteristics, without any well-marked lines of separation.* The difference in structure between tumors and physiological tissue is usually evident to the naked eye; but there are also tumors which so resemble the part from which they spring that the difference is only to be made out by the most exact examination.

Tumors that have well-defined boundaries are generally nodular (Fig. 188, *d*; Fig. 190, *d*, *e*; Fig. 191, *a*); and the size of the nodules varies, according to the character of the tumor and the stage of development at the time of examination, from the smallest visible speck to a mass of from twenty to sixty pounds or more. If nodular tumors grow on the surface of an organ they often take on the form of a sponge (Fig. 188, *d*) or of a polyp, and are named accordingly *fungous or polypoid tumors.* If a new growth develops on the surface of the mucous membrane or the skin, and the papillæ there present divide or new papillæ are developed, we have *warty, verrucose, or papillary tumors, or papillomata.* A further development of the papillary structure gives a *dendritic or cauliflower mass.*

The **structure of a tumor** *is determined by the tissue from which it grows;* and although true tumors always show an *atypical character*, yet they also possess certain features of their parent-tissues.

A great group of tumors is known as the **connective-tissue group.** These tumors are made up entirely of the connective tissues—fascia, cartilage, bone, fat, or mucous tissue—or of a tissue which is very like embryonic connective tissue, and therefore very rich in cells. The consistency and other characteristics of tumor-tissue are largely determined by the nature of the tissue existing at the site of its growth.

An *abundance of cells* gives a tumor a *soft appearance like marrow*, and hence the terms *medullary tumors* and *fungi medullares.*

The union of different sorts of connective tissue in one tumor gives us a *mixed growth.*

A second group of tumors is known as the **epithelial group.** These tumors possess a characteristic structure made up of *connective tissue and epithelial cells*, either of the *pavement variety* or *glandular.* As the epithelial elements for the most part lie in distinct groups in the meshes of the connective-tissue elements of the tumor, a structure is presented which suggests that of a gland; and the epithelial tumors receive, therefore, the name *organoid*, in opposition to the term *histoid*, which is given to the connective-tissue tumors, in which the structure of unformed connective tissue is imitated. But this distinction is not always an accurate one, as a connective-tissue tumor may also present an exquisite arrangement of stroma and parenchyma, which, on the other hand, may be wanting in an epithelial one.

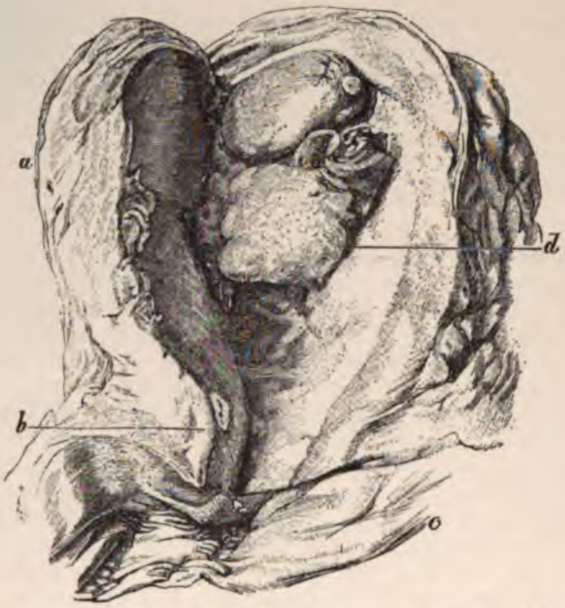


FIG. 188.—Spongy carcinoma of the mucous membrane of the posterior wall of the cavity of the uterus. *a*, Body of the uterus; *b*, Cervix; *c*, Vagina; *d*, Tumor. (Two-thirds life size.)

Excess of cells may also give a *medullary character* to tumors which belong in the epithelial group.

A third group of tumors is composed of **teratomata**—that is, tumors possessing a complicated structure, made up of different kinds of tissue. They are characterized by the presence of tissues which do not normally occur at the site of their growth.

Tumors usually **develop singly**; but it also happens that in a certain system of tissue, simultaneously or one after the other, there will appear a **great number of tumors** of the same sort, so that we must assume that the conditions requisite for the development of these tumors are present in the different parts of the system where they appear. Sometimes it happens that, at the same time, there appear in different parts of the body *two entirely different varieties of tumor*, which stand in no relation to each other, and whose simultaneous appearance is purely accidental.

The exact determination of what should be included under the term tumor is not easy, and consequently the word is used by different authors differently.

I hold it advisable, and warranted by the characteristics of the life of the new growths which we are about to consider, to exclude from tumors all hyperplastic swellings and all retention cysts which are purely retention cysts and show no independent tissue-development. And furthermore, according to my view, all increase of tissue dependent on the presence of parasites or infection is to be excluded from the domain of tumors; and so also should the infectious granulation growths which occur in connection with tuberculosis, syphilis, leprosy, etc., be excluded. If it should be proved—which so far has not yet been done—that some of the new growths now reckoned among epithelial tumors are caused by infection, then we must exclude these also from the category of true tumors.

Tumors similar in structure to the tissue whence they grow are often called *homœoplastic* (Virchow), while those to a marked degree unlike the parent-tissue are called *heteroplastic*, and are established as an especial group. Against any such classification must be mentioned the fact that the similarity between a tumor and the parent-tissue is never complete; for the true tumors (if we exclude simple hypertrophies) always show a certain amount of unlikeness—varying in different instances—to the parent-tissue.

§ 109. **All tumors develop by means of a proliferation of the existing tissue-cells, in combination with a new formation of blood-vessels.** An *emigration of leucocytes* often occurs at the same time, but this is by no means a necessary step in the development of tumors. Inside of the tumor the leucocytes are in part taken up by the tumor-cells, destroyed, and assimilated.

The processes of cell-division and development of blood-vessels are the same as those which have already been described in §§ 83 and 90; i.e., the division of nuclei is brought about through karyomitosis, and the vessels spring from sprouts given out by the proliferating cells of the old vessel-walls. The arrangements of fibrils (mitoses) occur for the most

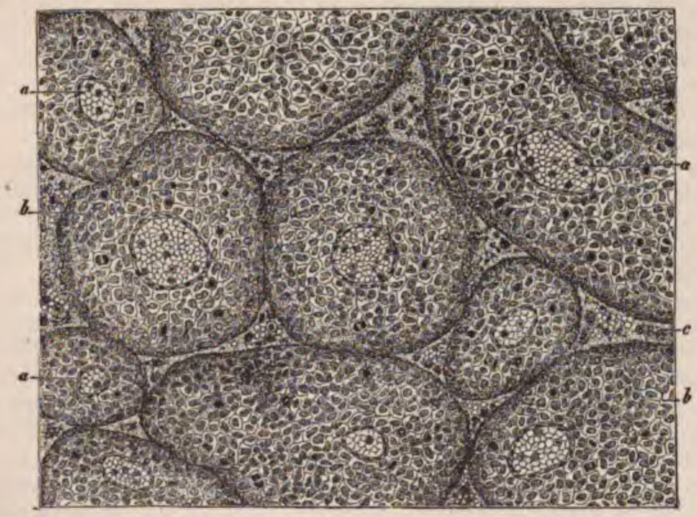


FIG. 189.—Section through a nodular angiosarcoma of the thyroid gland. *a*, Cross-section of a vessel; *b*, Perivascular cylinder of cells with numerous instances of cell-division; *c*, Horny masses with cells between the cylinders of cells. (Preparation treated with Flemming's acid-solution, stained with safranine, and mounted in Canada balsam. Magnified 80 diameters.)

part in typical forms (Fig. 189, *b*); but relatively often atypical forms—asymmetrical distribution of the fibrils (Hansemann, Ströbe), nuclei with abnormally large masses of chromatin (the so-called giant mitoses), multipolar mitoses, and forms showing pictures of the breaking up of nuclei (Arnold, Ströbe)—are encountered. The individual mitoses are scattered irregularly throughout the proliferating tissue (Fig. 189, *b*).

Tumors develop usually from small beginnings; seldom does their development start from a number of spots scattered diffusely throughout a whole organ. It results from this that the growth of the tumor does not produce an enlargement of the whole organ, but rather isolated nodules within it. Sometimes they grow very rapidly, sometimes slowly and with periods of inactivity. There is no limit to their growth, and they often reach colossal dimensions. Moreover, growth may cease for years and then suddenly begin again.

The **etiology of tumors** is by no means uniform, and often cannot be determined with certainty. But in most cases the conditions under which the new growth appeared can be given, and we may therefore, according to their origin, establish several groups of tumors.

One group of tumors arises from some localized predisposition of the tissues of a distinctly congenital nature, and we may therefore speak of them as *local malformations of tissue.* They either develop during intra-uterine life, and are therefore present at birth, or they develop during extra-uterine life, in the period of childhood or later; in which case traumatism not infrequently furnishes the immediate occasion for the beginning of the development of the tumors.

To this group belong the osteomata, chondromata, angiomata, fibromata (nerve- and skin- fibromata), sarcomata, and adenomata. A distinguishing characteristic of these tumors is the fact that they may be inherited.

We may include in a subdivision of this group those tumors which spring from *misplaced or transplanted tissue-germs*—i.e., from tissues which have been transplanted to some new situation during fœtal life. For example, we include in this category muscular or cartilaginous tumors found within the kidney, the testicle, or the parotid; lipomata found in the brain; and teratomata found in a great variety of organs.

A second group is developed after traumatic injuries of the tissues, and it is reckoned that such a traumatic origin can be definitely determined in from 7 to 14 per cent. of the cases. The cause may be a single injury, as a stab or a blow or a crushing or a fracture; or it may be a repeated mechanical irritation, like that due to rubbing, scratching, etc.

In a third group of cases the development of the new growth follows an inflammation, especially if accompanied by ulceration and the formation of a scar. This inflammation and ulceration may or may not owe their origin to some specific injurious influence. Cancer of the gall-bladder, for example (Fig. 190, *d*, *e*), occurs almost invariably in gall-bladders which contained gall-stones, and which therefore have been the seat of chronic inflammation. Cancer of the stomach may form in the edge of an ulcer or in its scar-tissue after it has healed. Sometimes cancer develops in the skin, or in the mucous membrane of the pharynx or larynx, in the base of a tubercular or syphilitic granuloma, or in the scar which follows one of these processes.

The tumors of a fourth group seem to owe their development to the unequal atrophy of the elements which make up a tissue, as a result of which certain

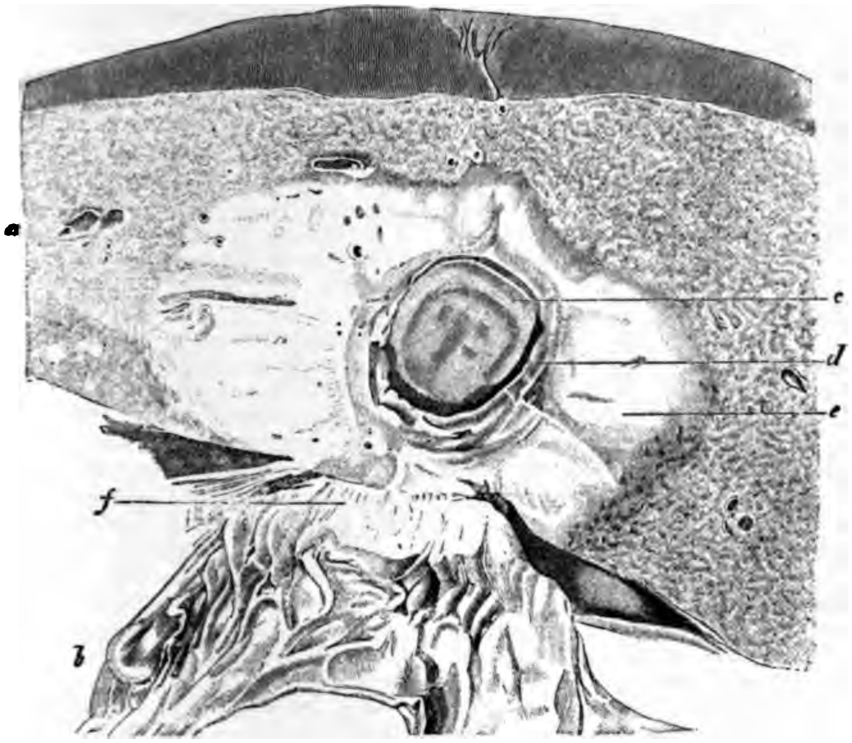


FIG. 190.—Primary cancer of the gall-bladder with an impacted stone in this cavity. Coronal section through the gall-bladder and liver. *a*, Liver; *b*, Duodenum; *c*, Gall-stone; *d*, Wall of the gall-bladder infiltrated with cancer; *e*, Cancerous infiltration in the neighboring liver-tissue; *f*, Portion of duodenum which is infiltrated with cancer and adherent to the rest of the new growth. (Life size.)

opposing forces are removed or lessened. This is especially true of epithelial growths (cancers), developed either in advanced age or in organs which, having just passed through a period of increased functional activity, are undergoing atrophy. In this way we can explain the development of cancer of the skin, for example, by saying that the connective tissue of the skin is undergoing a certain atrophy, which is connected with relaxation of its strata, while the epithelium is still possessed of its full power of reproduction.

Cohnheim formerly advanced the theory that all true tumors grew from distinct tumor-tissues, which were only persisting centres of embryonic tissue. This view receives no support, either from the results of clinical observation or from those of anatomical investigation of the tissues.

Recently the view has become wide-spread that new growths can be traced in large measure to infection by protozoa. Such an origin has been claimed particularly for cancer. But up to the present time there have been no discoveries capable of proving this view. Parasites can produce growths similar to the tumors, but we must not conclude that for this reason the true tumors are parasitic affections.

§ 110. When a tumor has arisen in any tissue it continues to grow independently, like a parasite. The tumor draws upon the vessels of the neighboring tissue for its nutrition, or it may grow independently by division of its own cells. In many cases the tumor increases only by **interstitial expansive growth,** and the neighboring tissues are simply displaced and pressed together. In other cases the tumor **grows by infiltration,** and forces its way into the intercellular spaces of the surrounding tissues, so that new territories are thus brought under the influence of the tumor. By this process a part of the cells of the invaded tissue are stimulated to proliferation, so that an increase of the tumor takes place by an **appositional growth,** in which the cells both of the tumor and of the surrounding tissue take part.

The characteristic feature of growth by infiltration consists in the *involvement, in the disease, of the tissues or organs which bound the original site of the tumor.* Moreover, *the tissue of organs which are simply adjacent to the organ originally affected may become involved by contiguity* (Fig. 190, *e*, *f*). If tumor-cells find an entrance into any of the larger cavities of the body, they may spread on its surfaces and lead to the development of tumors.

If, in the process of infiltrative growth, a tumor breaks into a lymph-vessel or a blood-vessel—something which happens in tumors called carcinomata and sarcomata—and if *cells of the tumors possessed of the power of development* escape into the vessel, **tumor metastases** are likely to follow; that is, there is likely to be a development of disconnected **daughter-tumors.** These secondary tumors may develop in the *lymph-vessels* of the organ in which the primary tumor has its seat (Fig. 191, *b*), but they usually develop rapidly in other organs as well: in the case of the lymph-vessels in the lymph-glands, and in the case of the blood-vessels in those organs to which the living cells are carried by the blood (cf. § 18).

The secondary tumors are developed directly from the transported cells. In *metastasis by the lymph-channels* the lymph vessels are first filled

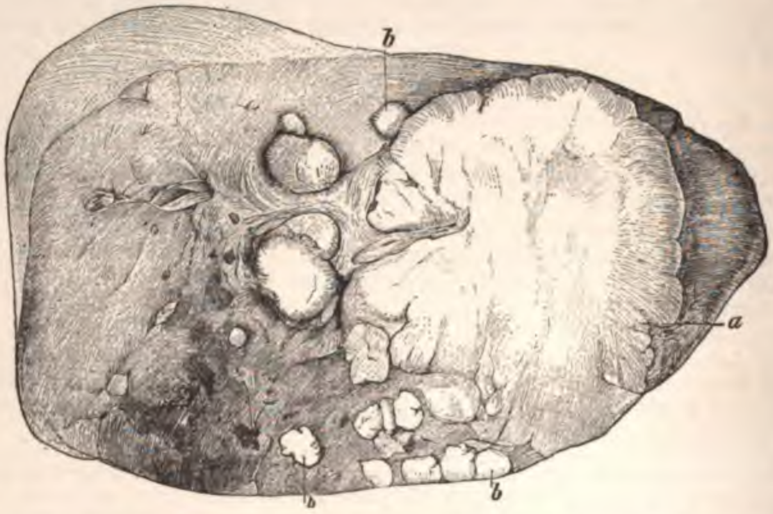


FIG. 191.—Section through a primary carcinoma of the liver, *a*, with multiple metastases, *b*, in the liver-substance. (Three-sevenths life size.)

with tumor-cells which have developed from the transported cells (Fig. 192). The surrounding tissue joins in this growth, new blood-vessels are formed; and in this way a tumor develops, usually in the form of smaller and larger *nodules;* but it may also happen that *the lymph-channels are more evenly distended by the growth* (Fig. 192), without any real formation of nodules; or at most little swellings occur in the course of the lymph-vessels. If the metastasis takes place in *lymph-glands*, these swell up into nodules of smaller or larger size, and the tumor-tissue gradually takes the place of the gland-tissue.

When the *metastasis takes place through the blood-vessels* the first development begins with the tumor-cells which form the embolus in artery, capillary, or vein; and under certain conditions the vessels, especially the capillaries (Fig. 193, *b*, *c*), may be filled throughout a considerable extent by the growing tumor-cells. The tissue in which the tumor embolus develops remains passive at first, and its specific components—e.g., gland-cells (*d*) and muscle-cells—undergo atrophy and finally disappear. Later, the blood-vessels and connective tissue take part in building up the secondary tumor.

In its further development the secondary nodule becomes sharply differentiated from its surroundings and increases in bulk. But often enough, at least in places, growth by infiltration persists, and under

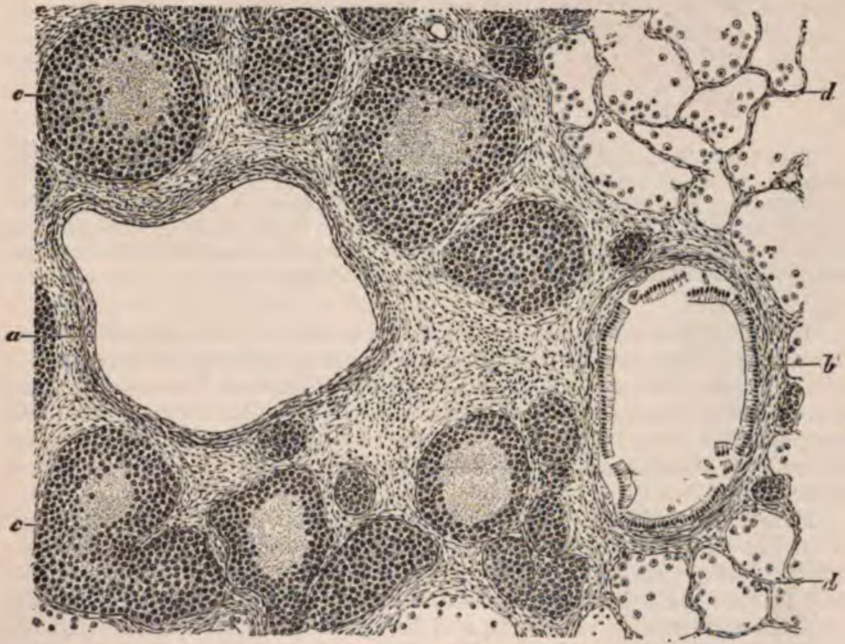


FIG. 192.—Metastatic carcinoma of the periarterial and peribronchial lymph-vessels of the lung, following carcinoma of the stomach. *a*, Artery; *b*, Bronchus; *c*, Periarterial and peribronchial lymph-vessels filled with tumor-cells; *d*, Pulmonary tissue showing single cells in the alveoli. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 25 diameters.)

proper conditions wide-spread diffuse tumors develop—as, for instance, in the liver (Fig. 193) and in bone-marrow.

The number of metastases taking place by lymph- or blood-channels varies greatly in different cases, and may be limited to one organ or may affect many. In rare cases the seeds of the original tumor may spread through almost the whole body, so that larger and smaller nodules appear in quick succession in the most diverse parts—in glands, muscles, skin, etc. This is possible when a tumor situated in the lung or in a bronchial gland breaks into a pulmonary vein.

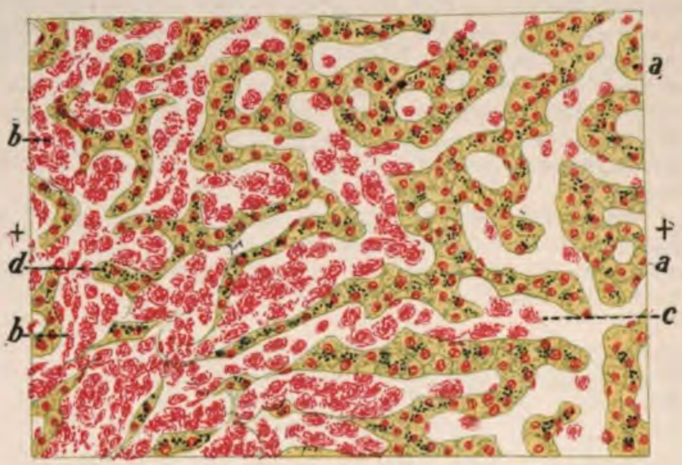


FIG. 193.—Metastatic sarcoma of the liver following primary sarcoma of the parotid. *a*, Broad framework of liver-cells; *b*, Sarcomatous tissue developed in the vessels; *c*, Single tumor-cells in the liver-capillaries; *d*, Framework of liver-cells which have undergone atrophy and fatty degeneration. (Preparation treated with Flemming's solution, stained with safranine and picrocarmine, and mounted in Canada balsam. Magnified 150 diameters.)

If a bit of tumor capable of forming metastases be transplanted from one animal to another of the same species, it sometimes happens that it will develop in the second animal. We may therefore have such a thing as *a metastasis from one animal to another*. In a similar way we may have, in operations upon man, transplantation of bits of tumor from one part of the body to another, and these may continue their growth in the new situation.

Side by side with the progressive development of tumors we find very often indeed **retrogressive changes**; and especially in rapidly growing cellular tumors, which increase by infiltrating the surrounding tissues, we may find, to a marked degree, fatty or myxomatous degeneration, pigmentation, necrobiotic changes, and hæmorrhagic infarction, so that the *tissue often sloughs completely*. The destruction of the cells in nodular tumors, in case it is followed by a resorption of the products of degeneration, may lead to *shrinking and the formation of cicatricial contractions.* Very often, too, we find *cysts containing the products of degeneration*, and even *ulcers;* and in the case of carcinomata of the mucous membranes, the parts of the tumor which grow up above the surface are apt eventually to disintegrate and disappear. Retrogressive changes usually do not occur in slowly growing dense tumors.

Necrosis and disintegration of the tumor-tissues seldom terminate in a **cure.** This is most likely to happen if a polypoid new growth becomes totally necrotic (for example, as a result of twisting of its peduncle) and sloughs away. Usually in tumors which have a tendency to undergo retrogressive changes and to disintegrate, while the older portions are falling to pieces, the tumor is constantly growing at the periphery and constantly involving new tissues.

If a tumor is extirpated, recovery may take place; but to insure this all parts of the tumor must be removed or destroyed. This is most readily accomplished in the case of slow-growing tumors which grow by expansion and have sharply defined borders. In tumors which grow by infiltration it is very difficult to define the limit of the tumor, which often extends far beyond the point where any change in the tissue is apparent. Consequently, in such cases, sooner or later a **recurrence** is apt to take place in the operation scar, the recurrence growing from portions of the original tumor which were not removed (Fig. 194, *a*). Such recurrences behave exactly like the original tumor, and can also form metastases (Fig. 194, *b*, *c*).

Tumors are usually classed as **benignant** and **malignant**, according to their clinical and anatomical characteristics. The benign tumors, as a rule, grow slowly by expansion, and do not form metastases. The malignant tumors, on the other hand, grow rapidly and by infiltration, undergo degenerative changes more readily, and give rise to metastases. The malignant tumors, generally speaking, are the carcinomata and sarcomata. It must be remembered, though, that the malignancy of a tumor depends on its location as well as on its nature. Thus a benign growth can cause malignant symptoms if its presence interferes with the functions of vital organs. So, for example, every tumor of the brain or of its membranes becomes a dangerous affection at the moment when it interferes with the functions of the brain; and such benign tumors as fibromata of the uterus, for example, as soon as they grow large enough to press upon and displace other organs, must be looked upon as destructive growths.

When a tumor has existed for a certain period there often is produced an appreciable falling off of nutrition in the body—a marasmus, commonly called the **cachexia of tumors.** This

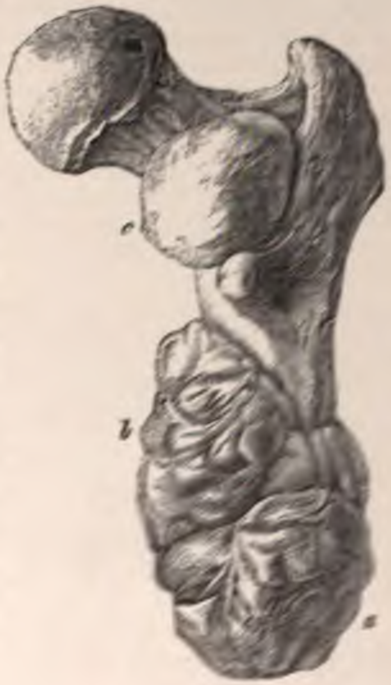


Fig. 194.—Sarcoma recurrent in the stump of a femur after amputation. *a*, Fungous tumor springing from the bone-marrow; *b*, *c*, periosteal nodules. (One-half life size.)

occurs for the most part in connection with the malignant growths called cancer and sarcoma, and may be caused, at least in part, by the great demands which the rapid growth of these tumors and their metastases make upon the nutritive supply. A still more important cause may lie in the fact that the tumor may interfere with the nutritive processes. For example, in carcinoma of the œsophagus, stomach, or intestine, the function of the affected organ is profoundly interfered with, and the assimilation of food may be almost completely prevented. It must be further observed that, by the degeneration of the tumor and the continuous secretion from the resulting ulcers, often a great deal of albuminous material escapes from the body; while from the putrefactive processes substances are often formed which, when absorbed, act injuriously upon the system. Finally, the pain which is often experienced in a tumor may rob the unfortunate patient of his sleep. Whether the tumor itself, in certain cases, manufactures substances which are poisonous to the body in general is unknown, but the possibility of such a thing cannot be denied.

II. The Different Varieties of Tumors.

1. *Tumors which Develop from the Middle Embryonic Layer.—Connective-tissue Tumors.*

(*a*) *Fibroma.*

§ 111. A **fibroma** is a tumor composed of *connective tissue*. It is usually in the form of a *node*, sharply differentiated from the surrounding tissue; usually it affects only one part of an organ, but in exceptional cases it may convert an entire organ into a single great mass of tumor. If it occurs on the free surface of a mucous membrane or the skin, it often forms a *papilloma*.

The consistence of the fibroma depends on the character of the connective tissue. It is often hard and tough, creaks under the knife (*desmoid tumor*), and presents, when cut, a white tissue much like tendon; and in other cases it is soft and flaccid, presents a grayish-white cut surface, and is somewhat translucent. In still other cases the bands of connective tissue are white and glistening, yet the tumor as a whole is more open in its structure and is correspondingly flaccid.

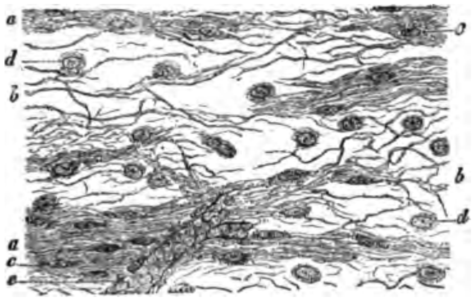


FIG. 195.—Section through an œdematous fibroma of the uterus. The bundles of connective-tissue fibres, which lie close together at *a*, are pressed apart at *b* by the fluid; *c*, Spindle-shaped cells; *d*, Swollen round cells; *e*, Blood-vessel. (Preparation treated with osmic acid and mounted in glycerin. Magnified about 200 diameters.)

There are all gradations between these hard and soft extremes, and even in one tumor different parts may possess different characteristics.

The hard kinds, as seen through the microscope, appear to be chiefly composed of thick bundles of coarse fibres (Fig. 195, *a*), among which are sprinkled a larger or smaller number of cells. If obstruction of the circulation and œdema supervene, the bundles of fibres (*b*) may be pressed apart, and the cells (*c*) which lie upon them may become swollen (*d*). By reason of these changes the tissue is rendered softer.

The softer kinds of fibroma, which present a translucent, gray-white surface on incision, are usually richer in cells; so that it is possible, by tearing a bit of the tissue to pieces, to isolate spindle-shaped cells (nuclei with tails). The intervening tissue is relatively less; the fibrillæ are more tender and are arranged in narrower bundles. Sections through such tumors, when stained, appear full of nuclei (Fig. 196, *b*).

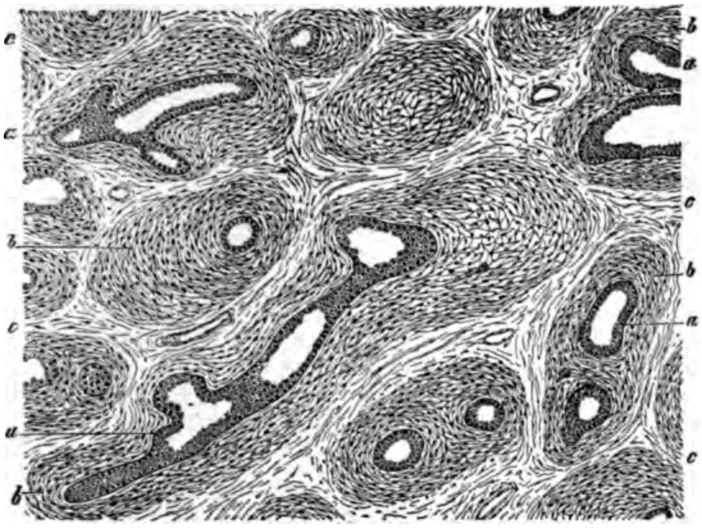


Fig. 196.—Pericanalicular fibroma of breast. *a*, Tubules of gland; *b*, Pericanalicular connective tissue, newly formed and full of cells; *c*, Connective tissue with few cells. (Specimen hardened in Müller's fluid and alcohol, stained with alum carmine and eosin, and mounted in Canada balsam. Magnified 40 diameters.)

The fibromata develop from actively growing cells of the connective tissue, and usually it is possible to find places which are richer in cells than the mass of the tissue, and in which the cells appear not only as small spindles, but also as round cells, or as short, thick spindles, or even as star-shaped cells. The change from this new-formed tissue rich in cells to mature connective tissue is brought about in the same way as was described in the chapter relating to Hyperplasia of Connective Tissue.

Fibromata may occur in any tissue which contains connective tissue in any form. They are very common, for example, in the nerves, skin, periosteum, fasciæ, and uterus, and less common in the ovary, mamma, intestinal tract, bladder, etc. In the mamma the fibromata develop especially around the canaliculi, so that the latter are found to be surrounded by connective tissue rich in cells (Fig. 196, *b*).

Fibromata do not form metastases, but a number of them often occur together, especially along the course of nerves or in the uterus. Moreover, it is not uncommon to see several centres of growth in a single tumor; that is, the mass of the tumor is made up of several nodules or bands which are separated from one another by ordinary connective tissue (Fig. 196, *b*). Fibromata are dangerous only by reason of their size or their position.

Fibromata may undergo fatty degeneration, or may soften and disintegrate, so that cavities are formed inside of them. These may also break through, and so give rise to ulcers. Occasionally fibromata also become calcified in part (fibromata of the uterus). The blood-supply varies greatly, and is sometimes abundant, sometimes scanty. Sometimes the blood-vessels are dilated, so that throughout the tissue there seem to be large canals or clefts, from which blood escapes when the tumor is examined in a fresh state. Dilated lymph-channels are also sometimes observed.

If the basic substance of a fibroma be strongly saturated with fluid, and the fibrillæ pressed apart, we have an *œdematous fibroma*, closely resembling the umbilical cord in appearance.

(*b*) *Myxoma.*

§ 112. A **myxoma** is a tumor consisting chiefly of *mucous tissue*, and is made up of cells and a liquid or gelatinous intercellular substance. The cells are for the most part of irregular shape, and are provided with processes of varying length (Fig. 197) which anastomose with one another (Fig. 198, *a*). The tissue is markedly translucent, soft, and shows plainly its blood-vessels when they are filled with blood. Gelatinous masses or a tenacious fluid, both of which swell up in water, may be obtained from the cut surface.

No tumor is ever completely made up of myxomatous tissue; it is found usually in combination with other kinds of tumor-tissue, especially with connective tissue, fat, cartilage, and sarcomatous tissue. For this reason the tumors are called **fibromyxomata, lipomyxomata, chondromyxomata,** and **myxosarcomata** (Fig. 198).

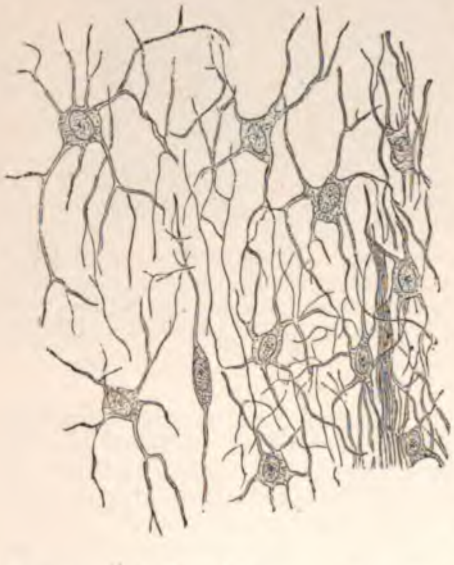


FIG. 197.—Cells from a myxoma of the periosteum of the femur. (Gold preparation. Magnified 400 diameters.)

Myxomatous tissue may be developed from fibrous tissue, this transformation being due to the fact that a fluid containing mucin collects in the meshes of the fibrillæ and then gradually causes the latter to disappear. When adipose tissue becomes myxomatous the fat disappears from the cells, which then grow small and become star-shaped, while a jelly-like material containing mucin appears between the cells. When cartilage is transformed into myxomatous tissue a mucoid degeneration takes place

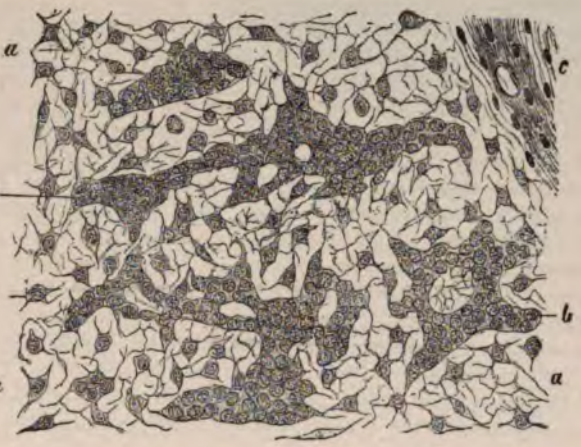


FIG. 198.—Section of a myxosarcoma. *a*, Mucous tissue; *b*, Strings of cells; *c*, Fibrous tissue. (Preparation stained with carmine and mounted in glycerin. Magnified 250 diameters.)

in the basic substance, while the cells change their shape (cf. Fig. 145). Myxosarcomata (Fig. 198) may develop out of myxomata through an increase in the proliferative activity of certain groups of cells, or they may develop from sarcomata through the accumulation of mucus between the cells of the tumor.

Myxomata, myxofibromata, and myxolipomata are developed most frequently in the connective tissue of periosteum, skin, fasciæ, and sheaths of muscles, or in subcutaneous and subserous fatty tissue, or in bone-marrow. Myxochondromata occur in the parotid, and are even quite common there.

They are always benign tumors, forming no metastases. Myxosarcomata, on the other hand, have the characteristics of sarcomata, and consequently may form metastases.

(*c*) *Lipoma.*

§ 113. A **lipoma** is a tumor composed of *adipose tissue.* These tumors are sometimes soft, sometimes solid, usually nodular and lobulated, and they often reach great size. Their structure is very like normal subcutaneous fat-tissue; that is, they are composed of lobules of fat, which are held together by thicker or thinner connective-tissue septa.

Microscopically, too, a lipoma greatly resembles the lobules of subcutaneous fat, although the cells are usually of greater size in the former. If fat-tissue and mucous tissue grow together, as often happens, the tumor is then called a **lipomyxoma**; or if there is a great deal of fibrous tissue it is called a **lipofibroma** or a **fibrolipoma.**

Usually lipomata develop from fat-tissue, but they may also grow from connective tissue that has normally no fat—e.g., from the submucosa of the intestine. Calcification, necrosis, gangrene, and sloughing may all occur in large lipomata. These tumors do not form metastases, but sometimes many of them appear at one time. A complete disappearance of a lipoma does not occur, even when the individual undergoes a marked general loss of flesh.

Lipomata are sometimes observed even in new-born children, as, for instance, in those cases where they are found in or over the clefts belonging to spina bifida; but they much more often develop for the first time in later years. The favorite seats of these growths are the subcutaneous tissues of the back, buttocks, neck, axilla, abdomen, and thigh; but they may also be found in the connective tissue separating individual muscles, in the adipose tissue of the abdominal cavity, in the kidneys and the mamma, under the aponeurosis upon the forehead, in the meninges, in the hand, fingers, etc. A rare condition, which occurs in men, is that which is characterized by a new growth of fat on the neck and throat. This condition, which has been described particularly by English authors, manifests itself in the form of knobbed and lobulated alterations of the skin in this region. Madelung, who has recently investigated the matter carefully, gives to the condition the name of *fatty neck*. The development of fat in these cases takes place partly in the subcutaneous tissue and partly in and under the fasciæ and between the muscles.

(*d*) *Chondroma.*

§ 114. A **chondroma** or **enchondroma** is a tumor consisting essentially of *cartilage*. The amount of connective tissue found in its structure, covering its surface or penetrating its interior as a framework for the blood-vessels, is so slight as to be quite lost sight of when compared with the cartilaginous tissue.

Cartilaginous tumors are usually developed in those places in which cartilage is found normally—that is to say, in some part of the osseous system or in the cartilaginous parts of the respiratory apparatus; but they do occur in tissues which normally have no cartilage, as, for example, in the parotid gland or in the testicle—more rarely in other organs. They may develop in bones, from remains of cartilage left intact at the time of ossification; but they are more apt to arise in the marrow or in the periosteum. These tumors vary greatly in size. The small ones are usually spherical in shape; the larger ones knobbed or lobulated. The individual nodules are separated from one another by connective tissue. Several of them often occur at the same time, particularly in the hands and feet, although they may also develop in other parts of the skeleton.

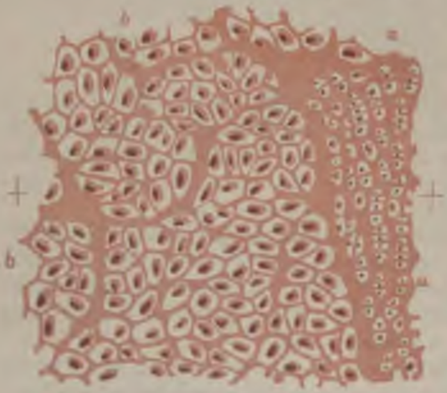


FIG. 199.—Section through a chondroma of the ribs. Cartilage containing many cells: *a*, Small; *b*, Large. (Preparation stained with hæmatoxylin and carmine, and mounted in Canada balsam. Magnified 80 diameters.)

The tissue of an enchondroma is usually that of hyaline cartilage (Fig. 199); less often is it composed of reticular or fibrocartilage. Still there are often fibrous patches in the hyaline cartilage. The periphery is often composed of fibrous tissue, which constitutes a sort of perichondrium.

The number, size, form, and arrangement of the cells vary greatly in different enchondromata, and also in the same tumor. Certain ones contain many cells (Fig. 199), others few; then, again, some have small cells and others large; and others still have both large and small cells.

The cells themselves have sometimes capsules and sometimes none; sometimes they lie in groups in a mother-capsule, sometimes the individual cells are scattered about in a regular manner. All the varieties of cartilage which exist normally may be found in tumors. Accordingly we find cells of different forms, the majority of them, however, being of the round form. Nevertheless it is common enough to find spindle- and star-shaped cells, especially in the neighborhood of the connective-tissue bands which separate the tumor into lobules or surround it as a whole. What was said in § 91 holds good here with reference to the method of development. Sometimes cartilage forms the matrix, sometimes bone-marrow, or periosteum, or bone, or one of the forms of connective tissue. Cartilaginous tumors growing from cartilage have been denominated *ecchondroses*.

The tissue of enchondromata is often subject to retrograde metamorphoses. Some of the cells often contain fat-drops. In large tumors the basic substance often undergoes a mucoid degeneration and becomes fluid. The result is either the formation of *mucous tissue* (§ 127, Fig. 236), thus giving rise to a chondromyxoma; or the intercellular substance undergoes complete liquefaction and the cells are destroyed, in which case *cysts* with fluid contents are formed—the result of softening processes. In other cases cartilage calcifies, or genuine *bone* may be formed, so that the name **osteochondroma** must be employed in designating such a growth. By excessive proliferation of the cells of the cartilage, sarcomatous tissue may result, and the neoplasm becomes a **chondrosarcoma** (cf. § 127).

An enchondroma is usually a benign growth, although in certain cases of mixed tumors metastases may occur.

(*e*) *Osteoma.*

§ 115. An **osteoma** is a tumor consisting of *bone*. Tumors of this nature are generally found in connection with the osseous system (Figs. 200–202), but they may occur elsewhere.

New growths of bone in connection with a normal bone have been variously designated according to their location and relations. If a new growth of bone is diffusely spread out it is called a *hyperostosis*. If it is confined to a limited area it is called an *osteophyte*, or if of considerable size, an *exostosis*. Circumscribed bony growths inside of bones are called *enostoses*. New growths of bone which are not attached to old bone are of four sorts: *movable periosteal exostoses*, which are surrounded by the tissues of the periosteum, but are separate from the bone; *parosteal osteomata*, which have their seat near a bone; *disconnected osteomata*, which are removed to some distance from any bone and are situated in tendons and muscles; and finally, *heteroplastic osteomata*, which occur in the lungs, meninges, diaphragm, skin (very rare), parotid gland, etc.

The teeth, too, may have excrescences. If they are formed from the enamel they are called *dental osteomata;* if from the dentine, *odontomata.*

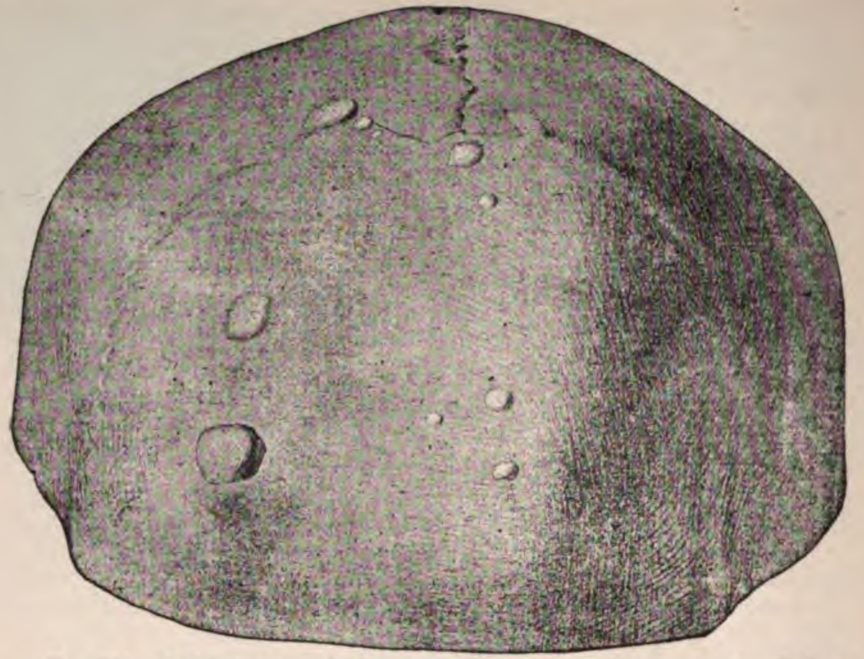
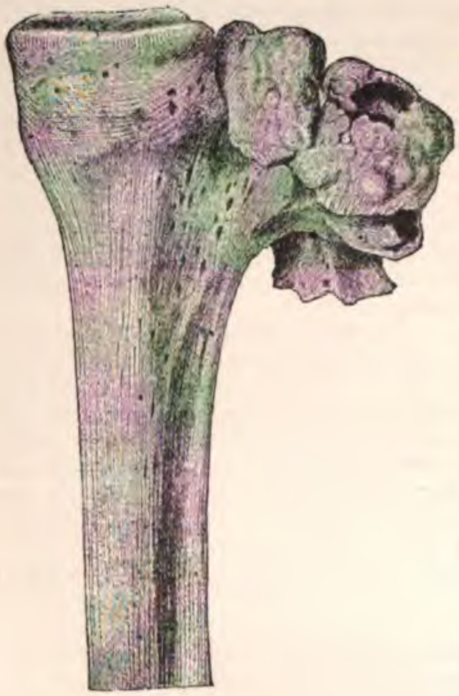


FIG. 200.—Multiple eburneous exostoses of the frontal bone. (Reduced about one sixth.



The latter come from a hyperplastic development of the pulp during the formation of the tooth.

We can divide osteomata into hard or *eburneous* (*osteoma durum* or *eburneum*) (Figs. 200 and 202) and softer *spongy forms* (*osteoma spongiosum* or *medullare*) (Fig. 201). The former consist of a firm, compact tissue like the cortical portion of the shafts of long bones, and have very narrow nutrient canals (Fig. 202); the latter are made up of thinner and more delicate masses of bone-tissue with wide medullary spaces, imitating in their structure the cancellous tissue of bones.

FIG. 201.—Cartilaginous exostosis of the upper diaphysis of the tibia. (Reduced about one third.)

Sometimes the surface is regular and smooth, so that the whole tumor has the appearance of a ball or a knob on a stem; or it may be irregular, rough, and warty, so that it has no definite shape (Fig. 201). The former is the case with the ivory-like nodules which most commonly appear as exostoses on the skull (Figs. 200 and 202), while the latter is true of the spongy exostoses and the disconnected and heteroplastic osteomata, such as are observed, for instance, in the falx of the dura mater.

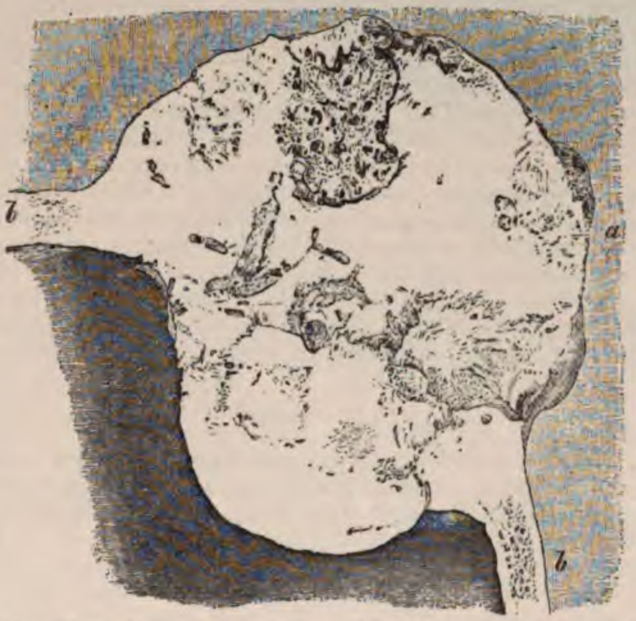


FIG. 202.—Eburneous osteoma of occipital bone, seen in a frontal section. *a*, Osteoma; *b*, Wall of cranium. (Eight-ninths life size.)

Osteomata occur either *singly* or in *multiple form*, and the latter mode of occurrence is rather common. The ivory-like exostoses of the skull (Fig. 200) and the osteomata of the dura mater often develop in great numbers, and circumscribed bony growths may form in large numbers on the bones of the trunk and lower extremities. In such cases the epiphyses or points of insertion of tendons, or both together, are the favorite seats. Such growths are evidently to be referred to an inherited disposition, on the part of the points affected, to overgrowth, or else to a disturbance in the development of the skeleton. Sometimes a transmitted tendency can be proved (cf. § 31).

The bony tissue is developed partly through the formation of osteoblasts, as described in § 91, partly through the metaplasia of formed tissues (§ 95). The matrix is formed chiefly from the connective tissue of the periosteum, as well as from that of the site whence the osteoma springs; also from the cartilage and the marrow. If an exostosis develops in such a manner that cartilage is first formed from the periosteum or the marrow, and then bone develops out of this, we apply to this the term *cartilaginous exostosis* (Fig. 201). But if this intermediate stage of cartilage is wanting, and the exostosis develops directly from the proliferating periosteum, then we term the growth a *connective-tissue exostosis* (Figs. 200 and 202).

Many of the new growths of bone which come under observation are not tumors in the strict sense of the term, but hyperplasias resulting from excessive growth or inflammatory processes. This is true of many hyperostoses, osteophytes, and exostoses, as well as of a part of the parostoses and disconnected osteomata. Scales of bone which in rare cases form in the mucous membrane of the air-passages are best explained as errors of development. The formations of bone which occur in the deltoid muscle and in the adductors of the thigh from constant carrying of a musket and horseback-riding must be looked upon as tumors which owe their origin to a local congenital predisposition; for the connective tissue belonging to muscles shows itself possessed of qualities which, as a rule, belong only to the periosteum and bone-marrow. The so-called myositis ossificans—that peculiar disease of the muscles which is characterized by a progressive ossification, in childhood, of their connective tissue—is to be interpreted in the same way (cf. Pathological Anatomy of the Muscles).

(*f*) *Angioma.*

§ 116. Under the name **angioma** are grouped *those new growths in the structure of which blood-vessels or lymph-vessels constitute such an important part as to determine the character of the tumor.* The vessels of such a tumor are only in part of new formation; the remainder are old vessels which have been more or less changed, these changes consisting of dilatations and hypertrophies of the vessel-walls.

Vascular tumors which arise from blood-vessels are called **hæmangiomata,** or *angiomata* in the restricted sense of this term; while those which arise from lymph-vessels are called **lymphangiomata.**

Hæmangioma simplex, or **telangiectasia,** are terms used to describe a formation in which there are an *abnormal number of normal blood-vessels,* or *abnormally broad blood-vessels,* or *capillaries and veins whose structure, in part at least, is abnormal.*

Such formations are commonly found in the skin. They are usually congenital, but grow after birth. They are called **vascular nævi** (*nævi vasculosi*), and are often found in places where fœtal clefts have closed (fissural angiomata). It is often impossible to speak of such a formation as a true tumor, for the skin may not be raised at all. But there are also telangiectases which deserve the name of tumor. In these not only the skin, but also the subcutaneous tissue, may be the seat of the disease; and in them, furthermore, the ectatic vessels are separated by connective tissue of new formation, and the tumor presents itself either as a sharply defined growth or merely as a thickening of the skin. The smooth nævus is a superficial substitution of another tissue for that of the skin. The color of the affected part is either *bright red* (*nævus flammeus*) or *bluish red* (*nævus vinosus*). Usually the line of demarcation between healthy and affected skin is not a sharp one. On the border of the chief mark or in its neighborhood are often little circumscribed red spots, presenting sometimes the appearance of outrunners from the centre of the disease.

The red color is produced by dilated vessels full of blood, which, situated either in the corium or in the subcutaneous tissue, form little sacs of blood. More rarely than in the skin do we find similar angiomata in glands (the breast), in bones, and in the brain and spinal cord and their membranes. On the other hand, we often find analogous alterations of the vessels in tumors—e.g., in gliomata or sarcomata.

The vascular changes consist for the most part of *circumscribed dilatations of preëxisting or new-formed capillaries* (Fig. 203). The dilatation is either fusiform or cylindrical or sacculated or spherical, or one of the endless possible combinations of these different forms. The larger blood-cavities communicate with one another by means of anastomosing capillaries of normal or moderately increased lumen. The vessel-walls are thin; that is, in comparison with normal capillaries, they are only slightly thickened.

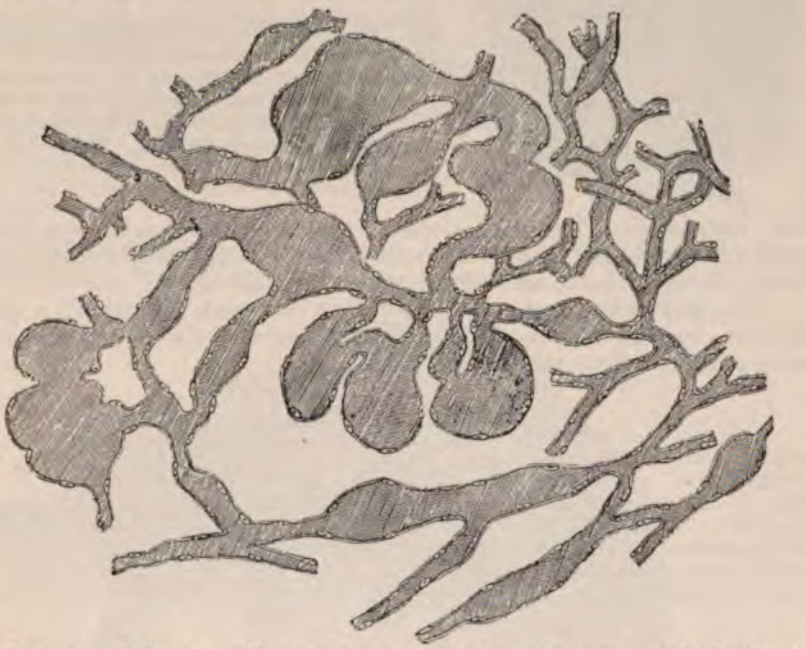


FIG. 203.—Dilated capillaries from a telangiectatic tumor of the brain, all the attached portions of tumor-tissue having been shaken off in water. (Magnified 200 diameters.)

Simple hypertrophic angioma is a term applied to a tumor composed of capillaries with dilated lumina and greatly thickened walls. It is most frequently found in the skin and subcutaneous tissue, where it produces a swelling much like a wart and often of about the same color as normal skin. The size of the vessels in this variety of angioma is not so great as in that already described; the vessels are, however, so numerous that in section they seem to lie side by side (Fig. 204), with but very little intervening tissue. The vessel-wall is disproportionately thick and rich in cells (Fig. 204), like the wall of an arteriole. In rare cases it is seen that the endothelia have become changed into cells rich in protoplasm, which protrude more or less into the lumen. If the vessel is empty and contracted as much as possible, and these cells happen to be disposed radially, the appearance presented is much like that of a section through the duct of a sweat-gland. The similarity is made even more striking by the fact that the tumor is composed of several nodules or lobules bound together by connective tissue, each of which is made up of a coil of hyperplastic vessels. Moreover, the lobules do actually sometimes inclose the duct of a real sweat-gland (Fig. 204).

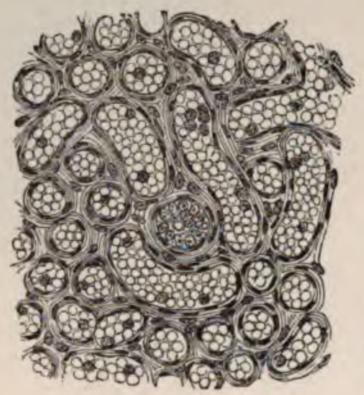
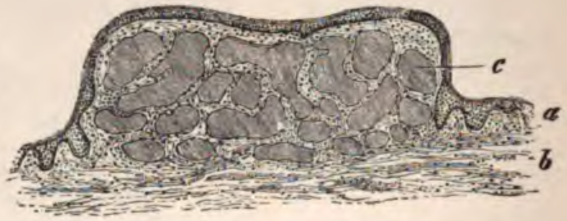


FIG. 204.—Section through an angioma simplex hypertrophicum cutaneum et subcutaneum. In the middle of the section is the duct of a sweat-gland cut transversely. (Preparation stained with alum carmine and mounted in Canada balsam. Magnified 200 diameters.)

If the ectasia is limited to a group of veins, while the capillaries belonging to them are slightly or not at all affected, we have an **angioma simplex venosum seu varicosum.** The dilatations of the veins are partly cylindrical, partly bottle-shaped, partly sacculated, the walls of the dilatations being easily distinguishable and sometimes even rather thick.

The **cavernous angioma,** or **tumor cavernosus,** consists of *a system of wide, variously shaped cavities* (Fig. 205) *separated from one another by mere connective-tissue partitions.*

FIG. 205.—Angioma cavernosum cutaneum congenitum. *a*, Epidermis; *b*, Corium; *c*, Cavernous blood-spaces. (Preparation stained with hæmatoxylin. Magnified 20 diameters.)



The partition-walls of the cavities are formed of nucleated connective tissue or of a tissue composed of spindle-cells, and at certain points there are openings by means of which communication may take place between two adjoining blood-cavities. The tissue is very like that of the corpora cavernosa of the penis. The cavities are lined with endothelium.

Cavernous tumors are usually situated in the skin and in the subcutaneous tissue, and they are sometimes found here at the time of birth (Fig. 205). They may also develop in these localities from simple angiomata by continual widening of the already ectatic blood-vessels. They generally occur in the form of raised patches of a bluish-red color, and sometimes the patch has a rough surface (*nævus prominens*). If the cavernous formation extends to any distance in the skin and subcutaneous tissue, we may have a deformed condition—suggesting *elephantiasis*—of the parts which are thus involved.

Among the abdominal organs the liver (Fig. 206) is most frequently the seat of cavernous tumors, which here form reddish-black foci, not elevated above the surface and not compressing the hepatic tissue, but simply playing the part of a substitute for this tissue. In this locality cavernous tumors are not congenital; they develop first in advanced life by varicose dilatation of single capillaries in an acinus, in association with a simultaneous atrophy of the liver-cells (Fig. 206). In the beginning there is no growth of the vessel-walls. Later, several capillaries unite to form a single cavity through partial atrophy of the separating walls. If the process extends to the border of an acinus, the periportal connective tissue forms a capsule for the otherwise ill-defined territory. Not infrequently the phenomena of new tissue-formation make their appearance at this stage.

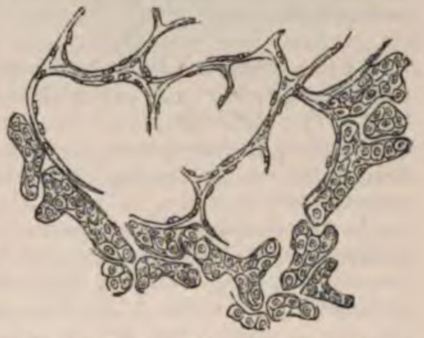


FIG. 206.—Section through the margin of a very small cavernous angioma of the liver, at a time when this margin was in process of active growth. (Carmine preparation. Magnified 150 diameters.)

Cavernous angiomata are very rarely found in the kidneys, spleen, uterus, intestine, bladder, muscles, bones, etc.

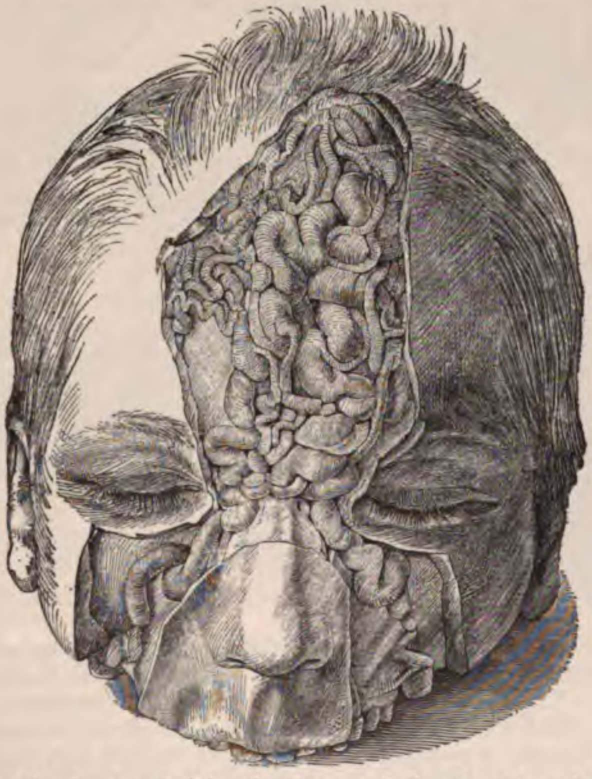


FIG. 207.—Angioma arteriale plexiforme of the frontal and angular arteries of both sides.

A **cirsoid aneurism**, or **angioma arteriale racemosum**, or **angioma arteriale plexiforme** (Fig. 207), is a condition in which the arteries of a whole group are dilated, tortuous, and thickened, so that they form a convolution of enlarged arteries. They feel to the palpating finger like a bunch of earthworms. Many of these angiomata, which are found particularly on the head, and which may cause erosion of bone, are congenital in origin; others appear to be acquired, and develop in consequence of a traumatism.

§ 117. **Angioma lymphaticum**, or *lymphangioma*, is composed of a tissue the greater part of which is made up of *dilated lymph-vessels* (Fig. 208). The different forms are: *lymphangioma simplex*, or *telangiectasia lymphatica; lymphangioma cavernosum;* and *lymphangioma cystoides.* The fluid contained in the cavities is usually a clear and bright lymph, but sometimes it is milky.

In the simple lymphangioma the lymph-vessels to a greater or less distance are dilated, and their walls are usually thickened. In the cavernous lymphangioma (Fig. 208) the vessels are still more increased both in number and in size, while the intervening tissue is diminished in quantity, so that even to the naked eye the tissue appears spongy. The cystic lymphangiomata contain cysts from the size of a pea to that of a walnut or greater. The tissue between the dilated lymph-vessels is, according to the part from which the tumor springs, connective tissue, or fat (Fig. 208, *c*), or muscle, or some other tissue. Sometimes this tissue includes foci of lymphadenoid tissue (*e*). Moreover, it may present the signs of active proliferation.

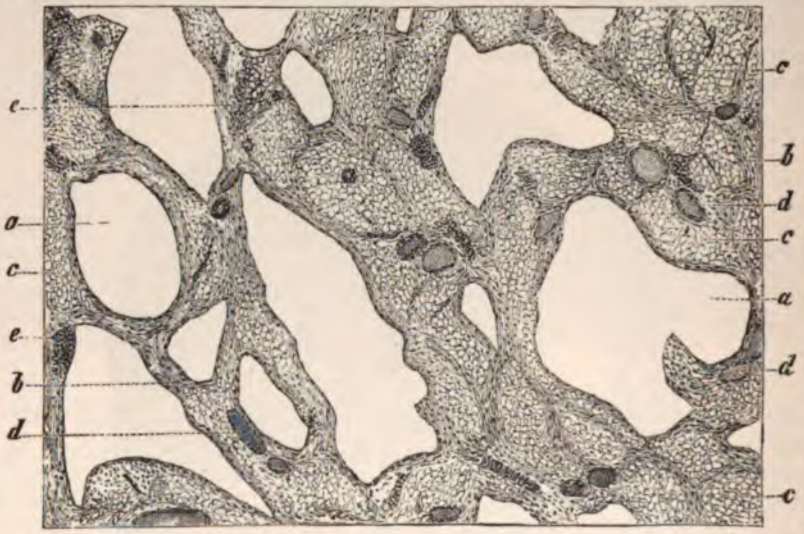


FIG. 208.—Lymphangioma cavernosum subcutaneum. *a*, Ectatic lymph-vessels; *b*, Fibrous tissue; *c*, Fat; *d*, Larger blood-vessels; *e*, Cellular tissue. (Preparation stained with alum carmine and mounted in Canada balsam. Magnified 20 diameters.)

Lymphangiomata are sometimes congenital, sometimes acquired. As a congenital phenomenon ectasia of the lymph-vessels is observed in different forms, particularly in the tongue (*macroglossia*), in the palate, in the lips (*macrocheilia*), in the skin (*nævus lymphaticus*), in subcutaneous tissue, in the neck (*hygroma colli congenitum*), in the vulva, etc. Lymphangiectasia of the skin is often also an acquired disease, as, for instance, in the thigh or the scrotum. Sometimes the lymphangiomata form large, well-defined tumors (Fig. 208), which fluctuate. If the cavernous development of the subcutaneous lymph-vessels spreads over large areas of the skin, conditions outwardly resembling those of *elephantiasis* may result. In such cases the intervening tissue usually takes part in the hypertrophic growth.

If the superficial dilatations in a cutaneous lymphangioma burst, lymphorrhœa may result. Ectasia of the lymph-vessels is often accompanied by connective-tissue hyperplasia of the skin or some other organ.

In very rare cases *chylangiomata*, containing chyle, appear in the course of the lymph-vessels of the intestine or mesentery. Cystic lymphangiomata of the peritoneum are also extremely rare.

Certain peculiar pathological formations in the skin, which are sometimes congenital and sometimes develop in the early years of life, and which are described as pigmented nævi, lentigines, ephelides, and fleshy warts, belong, according to their microscopical structure, to the *lymphangiomata*.

The *pigmented nævi* (*nævi pigmentosi*) (Fig. 209) form larger or smaller plaques situated on the same level with the surrounding skin (nævus spilus), or raised above it like warts (nævus prominens, nævus verrucosus), and often studded with hairs (nævus pilosus). They are pale brown or dark brown or black (Fig. 209), and are usually covered by normal, less often by hypertrophied epidermis. They are usually small, but they may be as large as an ordinary plate, and in rare instances they may cover a large part of the body.

Lentigines appear at any time after birth, and on any part of the surface of the body; and when once formed they remain for life. They closely resemble the little pigmented nævi, and form well-defined spots of a yellow or brown or almost black color, and as large as a pin-head or larger.

Freckles, or *ephelides*, are ill-defined, angular, pale-brown spots not elevated above the surface, which appear in the early years of life on face, hands, and

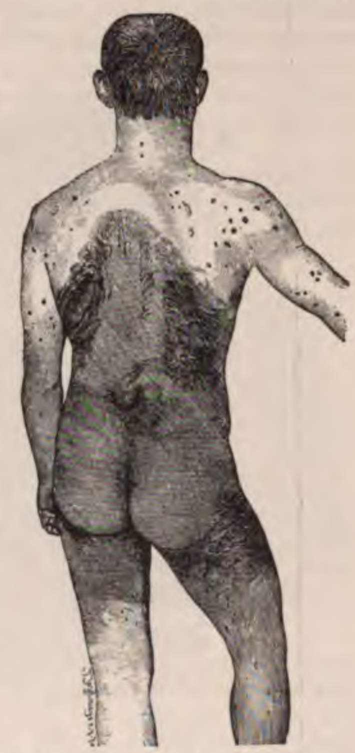


FIG. 209.—Large, hard pigmented nævus of the back, buttocks, and thighs, with scattered smaller pigmented spots on the upper part of the body. (After Röhring.)

seldom elsewhere, and which either remain permanently or in course of time disappear. The pigmentation is favored by the sunlight.

Fleshy warts (*verrucæ carneæ*) are non-pigmented, well-defined, smooth or slightly roughened (Fig. 210) or very uneven papillary growths caused by a normal or hypertrophic epithelium (Fig. 211, *a*).

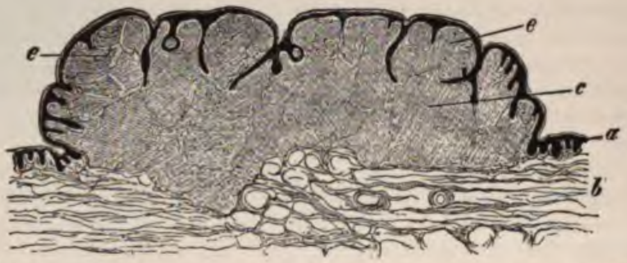


FIG. 210.—Section through a slightly uneven fleshy wart. *a*, Epidermis; *b*, Cutis; the cellular new growth at *c* is in the cutis; at *e*, in the papillæ. (Preparation stained with aniline brown. Magnified 10 diameters.)

In all of the pathological formations just described the connective-tissue framework incloses masses of cells, either in round groups or drawn out into bands. They lie partly in the papillæ and partly in the corium,

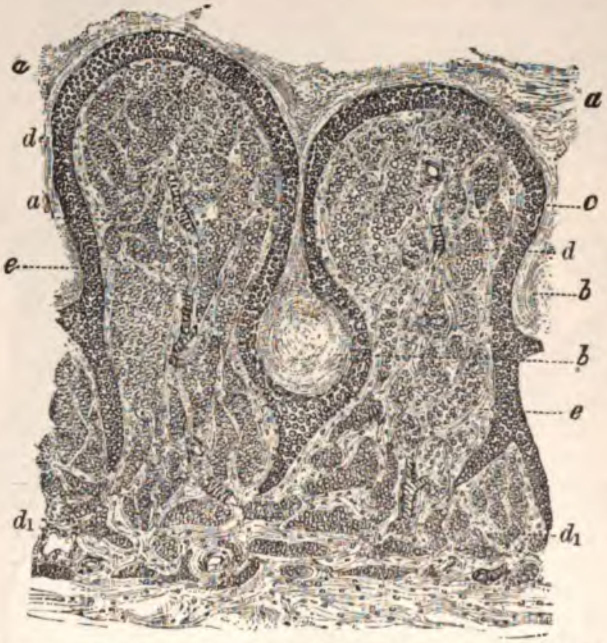


FIG. 211.—Section through two papillæ of a papillomatous fleshy wart. *a*, Thickened horny layer of epidermis; *b*, Epithelial pearls; *c*, Rete Malpighii; *d*, Nests and strings of cells in the papillæ; d_1, Nests and cells in the reticular layer; *e*, Connective tissue. (Preparation stained with carmine. Magnified 50 diameters.)

and are more abundant in those cases where the growth is elevated above the surface of the skin. In the pigmented growths these cells contain the pigment, usually in the form of yellow and brown granules, but also diffused throughout the substance of the cells.

So far as can be judged from the position and arrangement of the cell-masses, it seems probable that the cells are pathologically developed from the endothelial cells of the lymph-vessels; so that the growth can be reckoned with the lymphangiomata, and, under the name *lymphangioma hypertrophicum*, it may well be placed by the side of the hæmangioma hypertrophicum. In consideration of the marked endothelial proliferation which takes place in these cellular nævi, they might be classed among the endotheliomata or among the lymphangiosarcomata (cf. § 124); but the limited character of their growth militates against this classification.

(*g*) *Myoma.*

§ 118. **Myoma** is the name applied to a tumor whose chief structural elements are *newly developed muscular fibres.* An obvious division is into *leiomyomata* if the muscular fibres are of the smooth variety, and *rhabdomyomata* if the fibres are striped.

Leiomyomata, called also *myomata lævicellulares,* occur most frequently in the uterus, less often in the muscular layers of the alimentary canal or in those of the urinary tract. They are rounded nodular tumors like the fibromata. In exceptional cases they are found in the skin and subcutaneous tissue, where they form small nodules which only rarely attain the size of a pigeon's egg. They occur either singly or in larger number, and may appear in early childhood or even before birth (Marc).

If the new growth takes place in muscular organs it proceeds from the muscular layer, forming in its development bundles of muscle-fibres (Fig. 212) interwoven in various directions, and giving, therefore, in section a variety of views. In the skin and subcutaneous tissue, as far as there are any observations on the subject, the new growth of muscle-fibres has its origin in the muscularis of the vessels (Fig. 213), which not only becomes thickened (*e*), but gives off separate outrunners of muscular cells (*b*). This new formation of muscular tissue may easily be associated with the pathological formation of blood-vessels (*a*), so that tumors result, to which the name *angiomyomata* applies (Fig. 213). According to the ob-

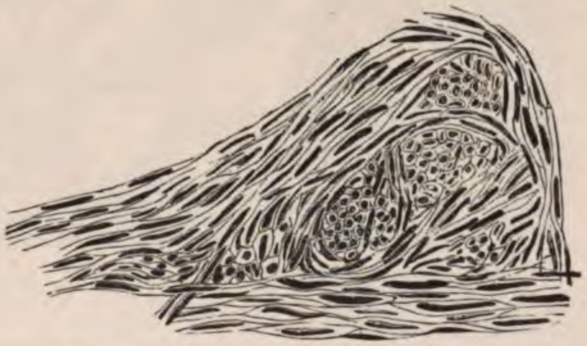


FIG. 212.—Section through a leiomyoma, showing the nuclei cut both longitudinally and transversely. (After Perls.)

servations of Jadassohn, myomata of the skin may also spring from the erector muscles of the hairs—the arrectores pilorum.

A certain amount of connective tissue takes part in the formation of a myoma, and often assumes such importance that the tumor deserves the name **myofibroma.** For example, most of the myomata of the uterus are myofibromata. The fibrous connective-tissue portions of the tumor appear glistening white, while the muscular parts are reddish white or bright reddish gray. The fusiform muscle-fibres may be isolated by teasing a fresh bit of tumor, or, better, a bit which has macerated for twenty-four hours in 20 per cent. sulphuric acid, or for twenty to thirty minutes in 34 per cent. potassic hydrate. In a longitudinal section the muscular fibres are best recognized by the staff-like nuclei (Fig. 212 and Fig. 213, *b*), as well as by the regular arrangement of the cells in bands or parallel lines. In cross-section the muscle-cells appear as little areas whose rounded boundary-lines are somewhat flattened by pressure one against the other, while in the centre of each of these areas is the nucleus cut transversely (Fig. 212).

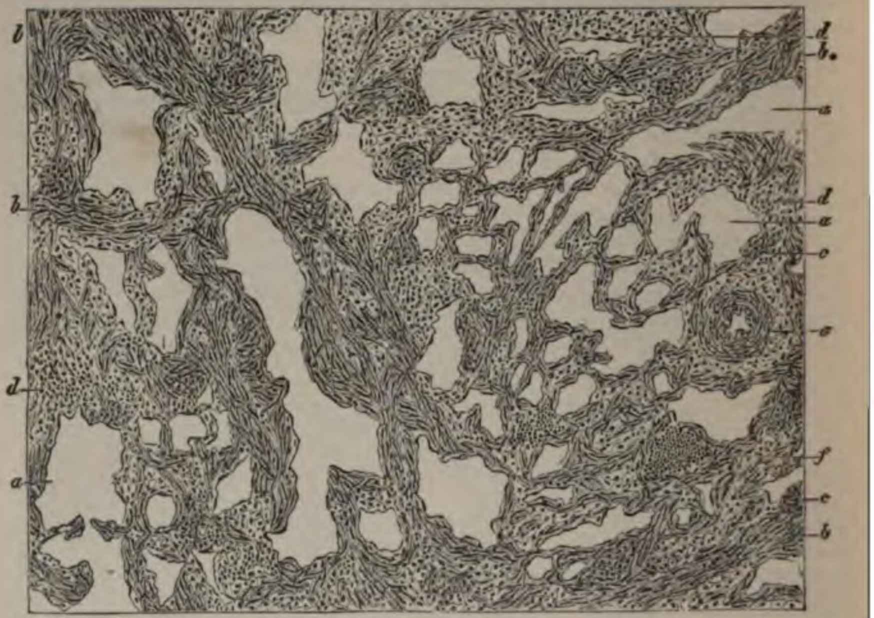


FIG. 213.—Subcutaneous angiomyoma of the back. *a*, Cavernous blood-vessels; muscular strings cut longitudinally at *b*, transversely at *c*; *d*, Connective tissue; *e*, Artery with hypertrophied muscular layer; *f*, Group of lymph-cells. (Preparation hardened in alcohol, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 50 diameters.)

Leiomyomata are thoroughly benign tumors. In fibromyomata of the uterus we often have processes of fatty degeneration and softening, which destroy the tumor or lead to the formation of cystic cavities. Calcification is also common. A myofibroma may become a pure fibroma by atrophy of the muscular fibres.

A **rhabdomyoma** (Zenker), or *myoma striocellulare* (Virchow), is a rare tumor whose essential part is made up of striated muscle-fibres either well or poorly developed. When well developed the muscular fibres form nucleated bands of various widths, which show a transverse (Fig. 214, *a*, *b*, *c*) and in places also a longitudinal striation (*e*, *f*). The ill-developed forms consist of narrow bands without transverse striation (*d*); of spindle-cells with long-drawn-out thread-like processes without transverse striation (*g*) or with partial striation (*f*); and also of rounder cells of different sizes, which show either a radial or a concentric striation (*h*, *i*). Besides these there are also cells which possess no especial characteristic, so that it is impossible to decide whether they are young undeveloped muscle-cells or simple cells of the connective tissue. The bands as well as the spindles are usually in bundles, and interwoven among themselves. It is usually not possible to demonstrate with certainty, on the surface of the fibres, a sarcolemma; but various delicate membranes have been described by different authors which apparently were fragments of a sarcolemma.

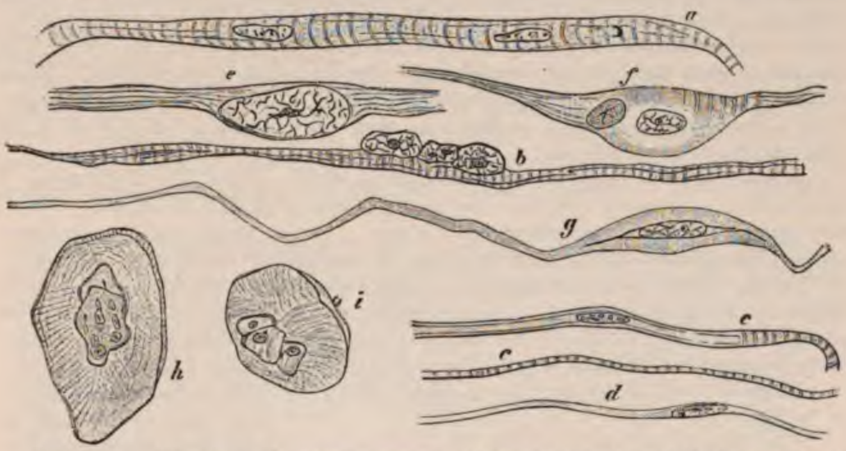


FIG. 214.—Cells from a rhabdomyoma. (After Ribbert and Wolfensberger.) *a*, *b*, *c*, Fibres of various sizes with transverse striation; *d*, Small nucleated fibre without striæ; *e*, Spindle-cell with longitudinal striæ; *f*, Spindle-cell with longitudinal and transverse striæ; *g*, Spindle-cell, non-striated, with elongated processes; *h*, *i*, Round cells with concentric and radial striation.

Rhabdomyomata occur most frequently in the kidney or in its pelvis, in the testicle and in the uterus; seldom in other localities, as, for example, in the vagina, bladder, muscles, subcutaneous tissue, mediastinum, œsophagus, etc. They form nodular tumors of varying size, and if situated on the surface of a mucous membrane the new growth is polypoid or papillomatous in shape. In the kidney and testicle they either form well-defined nodules or else they cause the destruction of the whole organ. The growth of these tumors is due apparently to misplaced portions of embryonic muscle-tissue, and consequently the condition is generally congenital. But these tumors may first develop at an advanced age. Sometimes another tissue—e.g., cartilage—is included in the tumor. Moreover, fairly well-developed muscular fibres are found in complicated tumors of the testicle and kidney.

If a tumor contains only a few cells which can be definitely recognized as muscle-fibres, while most of the cells have no specific character, it is usually called a *myosarcoma*.

(*h*) *Glioma and Ganglionic Neuroglioma.*

§ 119. **Gliomata** are tumors which grow from the *cells of the stroma of the central nervous system*, and which, when fully developed, consist essentially of these cells. In the brain they form growths which for the most part are not sharply defined from the normal brain-substance, but pass into the latter by insensible gradations. They often, therefore, convey the impression of a local swelling of the brain, and only the difference in color, and a comparison of the healthy with the pathological tissues, suffice to convince the eye that a real tumor is present. When they occur in the spinal cord these tumors are most apt to arise in the neighborhood of the central canal, and may spread over a considerable length of the cord.

Their appearance varies considerably: sometimes they are light gray, translucent, of about the color of the cortex, and moderately firm in consistency; sometimes they are grayish white and of firmer consistency; and at other times they may be reddish gray or dark red in color. In the latter case they are traversed in every direction by numerous dilated vessels. Gliomata which contain much blood often exhibit hæmorrhagic foci. Fatty degeneration, softening, and destruction of the tissue are also common occurrences.

A section of a fully developed glioma shows under the microscope a network of extremely delicate glistening fibres (Fig. 215, B), among which are embedded numerous short oval nuclei. A very scanty cell-protoplasm surrounds these nuclei, and can be distinguished only with difficulty. When the tissue is investigated in the fresh state or after maceration in Müller's fluid, it is easy to detect that these nuclei belong to cells that are characterized by the great number of fine branching processes which they possess, and which extend in every direction (Fig. 215, A).

The cells closely resemble normal ganglion-cells, although at times they are much larger, and, in some instances, more spherical in shape. A few of them contain two, three, or even four nuclei.

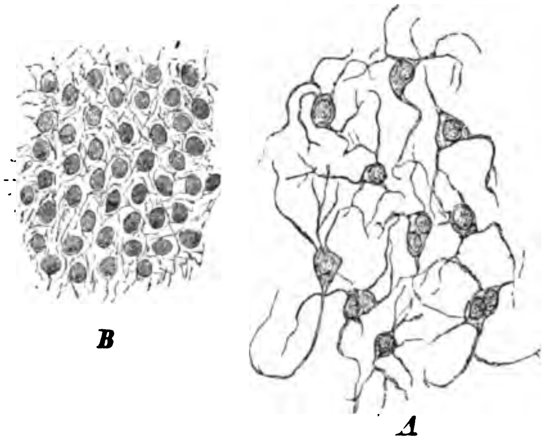


FIG. 215.—Glioma of the cerebrum. A, Cells isolated by teasing, and stained with carmine; B, Section from the same tumor after hardening in Müller's fluid. (Preparation stained with aniline brown and mounted in Canada balsam. Magnified 350 diameters.)

Investigations with reference to the development of gliomata have proved that the glia-cells are the mother-cells of the tumor. The ganglion-cells do not take any part in the proliferative processes. The abundance of cells in a glioma varies greatly. Sometimes the cells preponderate decidedly, and then at other times the stroma is the more prominent part of the texture. A simultaneous proliferation of the cells of the perivascular connective tissue produces a gliosarcoma.

The vessels are often developed to a very great degree, and in some places they may be ectatic.

Gliomata usually occur singly, and do not furnish metastases. Their etiology is unknown. Some gliomata probably originate from imperfectly developed portions of the brain and spinal cord. Traumatism may furnish the exciting cause for their development.

Certain highly cellular tumors which develop in the retina, and whose elements closely resemble the cells of the nuclear layer (*Körnerschicht*), are classed among the *gliomata*. As their growth advances they break through in part into the retrobulbar space, and in part forward through the cornea and sclera. They are apt to recur after extirpation, and they cause metastases. The cells of which they are composed are round, some with and some without processes. It is open to doubt whether these tumors should be classed with the gliomata. They ought rather to be reckoned among the sarcomata.

Neuroglioma ganglionare (Fig. 216) is a term applied to those new growths which arise in the *central nervous system*, are composed of hyperplastic *glia-tissue*, *ganglion-cells*, and *nerve-fibres*, and constitute either ill-defined swellings of the larger masses of the brain or circumscribed nodular enlargements of small sections of this organ. When examined

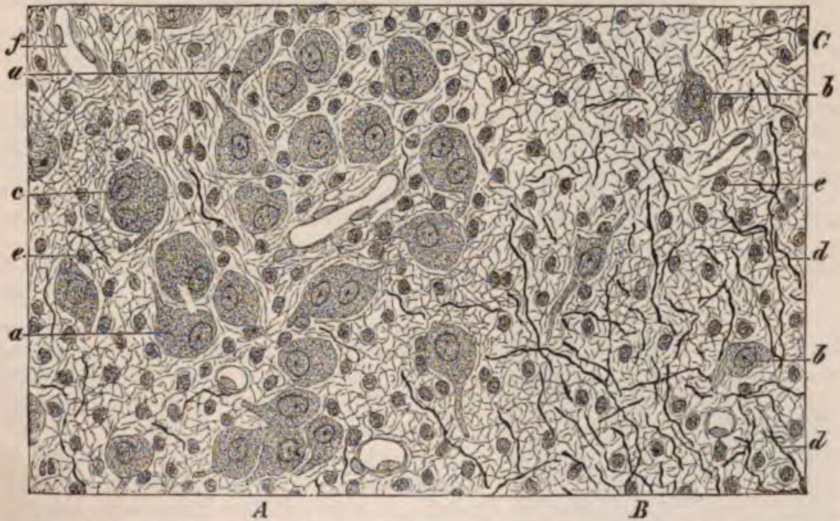


FIG. 216.—Section from a nodular neuroglioma ganglionare of the central convolution of the cerebrum. A, Portion of the tumor which is rich in ganglion-cells; B, Portion containing nerve-fibres; C, Jelly-like portion. *a*, Ganglion-cells in groups; *b*, Individual ganglion-cells; *c*, Ganglion-cells with two nuclei; *d*, Nerve-fibres with medullary sheaths; *e*, Glia-cells; *f*, Blood-vessel. (Preparation treated by Weigert's method and mounted in Canada balsam. Details completed from another preparation which had been stained with hæmatoxylin. Magnified 300 diameters.)

by the naked eye the affected portions of the brain may still appear to be fairly normal; but as a general rule the distinction between gray and white substance is fainter than normal, and the tissue is throughout white or grayish white or spotted white and gray, and at the same time more or less hardened.

These masses are chiefly made up of more or less dense glia-tissue containing a certain number of nerve-fibres (*d*) and ganglion-cells (*a*, *b*, *c*), not only in the region of the cortex, but also in that of the white substance.

Probably all such formations must be regarded as the result of a disturbance of the embryological development of the brain—that is, as local cerebral malformations, which have undergone further development after birth.

(i) Neuroma.

§ 120. The tumors called **neuromata** are observed most often in the ends of amputated nerves, where they form at times quite large swellings, which are either separated from the surrounding tissues by more or less sharply defined limits or are united to them without any such distinct line of separation. From their origin they have received the name of *amputation neuromata* (Fig. 217, *b*). The development of these neuromata is explained in the following manner: After the nerves are cut off, more or less connective tissue forms on the stump, and at the same time the axis-cylinders divide and grow out in length. In this manner the scar-tissue becomes supplied with nerves, which at first have no sheaths, but which very soon become covered with fibrous sheaths and ultimately with medullary ones. The mass of nerves penetrating into the granulation tissue may be very great, so that the connective tissue, after a certain length of time, may contain a rich supply of nerves, which, radiating from the end of the old nerve, spread through the fibrous tissue in every direction (Fig. 217, *b*). We have here, therefore, an instance of the useless regenerative growth of a nerve-stump—a growth which exceeds the physiological necessities of the nerve and so forms a tumor-like mass.

Another form of neuroma develops spontaneously in the course of a nerve, without any outside provocation. This tumor owes its origin to an *increase of the*

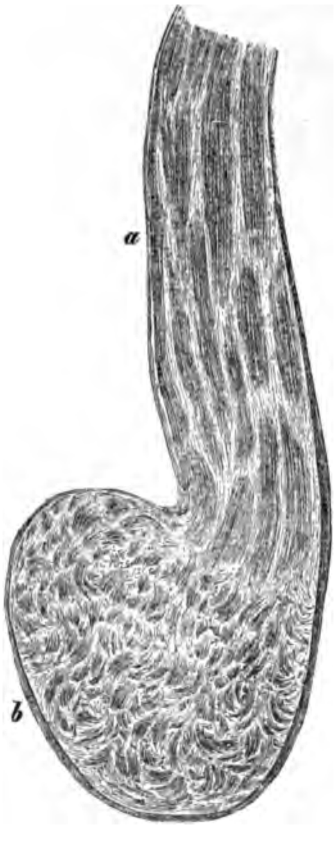


FIG. 217.—Amputation neuroma of the ischiatic nerve (nine years after amputation). Longitudinal section. *a*, Nerve; *b*, Neuroma. (Drawn from a preparation which had been hardened in Müller's fluid. Magnified 3 diameters.)

connective tissue of the nerve, usually of the outer, more rarely of the inner layers of the endoneurium; as a result of which the nerve-bundles, at the point where the tumor is developing, are inclosed in a more or less thick layer of connective tissue, usually of a loose sort (Fig. 218, *b*, *d*); or these bundles are split open by the growth of connective tissue into separate individual fibres. Sometimes the perineurium is also involved in the proliferative process. Where nerves lie together in a large bundle the epineurium as well as the endoneurium and perineurium of the smaller nerve-bundles may be affected by this process, but this is usually not the case.

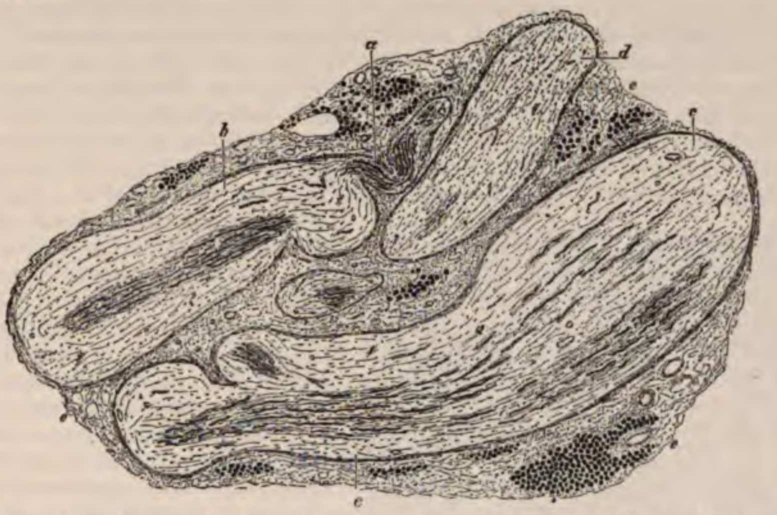


FIG. 218.—Nerves from a cirsoid neuroma which involved the cheek and lower jaw and presented a close resemblance to elephantiasis. *a*, *b*, Nerve, the outer layers of whose endoneurium have undergone decided proliferation; the nerve-fibres proper occupy the axis of the entire mass; *c*, Nerve with markedly proliferated endoneurium and separated nerve-fibres; *d*, Thickened nerve showing a small bundle of nerve-fibres at the left end; *e*, Loose connective tissue, rich in nuclei, lying between the nerves and containing fat-tissue. (Preparation hardened in Flemming's solution, stained with safranine, and mounted in Canada balsam. Magnified 8 diameters.)

These tumors, structurally considered, are not neuromata, but *fibromata of the nerves*. A number of them are usually present at the same time, and they may occur in all the peripheral nerves, although, as a rule, they are limited to a definite area of nerve-distribution. The nodules are sometimes situated along the nerve-trunk, sometimes on the finest branches, usually of the cutaneous nerves. These soft connective-tissue nodules, which are scattered about through the skin in smaller or larger numbers, are termed *multiple fibromata of the skin*. The finest nodules are demonstrable only with a microscope, but the usual size is from that of a pea to that of a hazel-nut. Individual tumors may reach the size of a man's fist, the nerve-fibres being quite lost sight of in the great mass of connective tissue, whose continued growth may even cause them to waste away entirely. In addition to this formation of well-defined nodules there may also be, throughout the area of distribution of the affected nerves, *a diffuse thickening of the nerve-fibres, due to hypertrophy of the connective tissue.* And finally, with the conditions mentioned may be associated a hypertrophic thickening of the connective tissue of the skin proper and of the subcutaneous tissue, resulting in *alterations of the skin not unlike those observed in elephantiasis.*

A third form of neuroma is the *cirsoid neuroma* (Bruns) or *plexiform neuroma* (Verneuil), a tumor which is characterized by the circumstance that in the domain of several nerve-branches a convolution of twisted and interwoven, thickened and nodular nerves takes place (Fig. 219). An examination of the individual cords reveals this also to be a *fibromatosis of the nerves*, the excessive growth of the endoneurium resulting partly in a diffuse thickening of the nerve-fibres, partly in a nodular one. But in this case attention should be directed to the fact that the nerves in the territory involved are not only thickened, but also actually *increased in length*, and consequently *rendered tortuous;* and, furthermore, that the nerves are *increased in number*, so that the sum total of the nerves situated in the skin and subcutaneous tissue is greater than it should be under normal conditions. The conditions here, therefore, are those of a genuine neuroma, a *neuroma verum.* Most of the nerves in this tumor are medullated (neuroma myelinicum). It is difficult to determine to what extent tumors of this nature contain nerve-fibres which are non-medullated (neuroma amyelinicum); nevertheless cases have been reported in which most of the fibres were found to be non-medullated. Cirsoid neuromata occur on the head, body, and extremities, and are usually characterized by *gross alterations of the skin which remind one strongly of elephantiasis.*

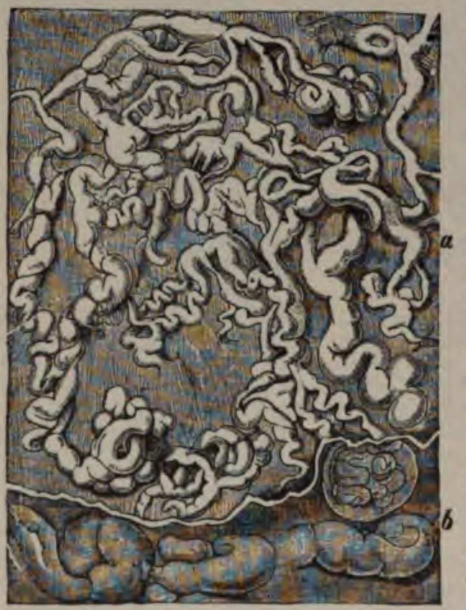


FIG. 219.—Cirsoid neuroma of the sacral region. (From a drawing by P. Bruns.) The nodular, twisted, and interwoven nerves are dissected out at *a*, while at *b* they are still covered by connective tissue. (Life size.)

Neurofibromata and cirsoid neuromata do not cause metastases, but in certain cases neuromata take on a sarcomatous and consequently a malignant character. *Hereditary transmission* and *congenital predisposition* have been proved to be concerned in both forms of neuromata.

(*k*) *Lymphadenoma and Lymphosarcoma.*

§ 121. The term **lymphadenoma** is applied to growths which represent a *proliferation of lymphadenoid tissue*—a proliferation which may lead to a considerable increase in the size of the lymphadenoid organs already existing in the body. Generally several such organs are affected at one time, as in the case of an entire group of lymph-glands; and when this is the case the process may extend, like a general disease of the body, over a smaller or larger portion of all the lymph-organs. The lymphatic glands, under these circumstances, increase in size until they are as large as a hazel-nut or a walnut, or even larger. In consistency these enlarged glands are soft, and their cut surface presents a white medullary appearance. The follicles of the spleen become transformed into nodules of considerable size. The tonsils attain the dimensions of more or less extensive tumors. The lymph-follicles in the mucous membranes stand out more prominently above the surface, and may also attain the proportions of considerable nodules.

The increase in bulk is chiefly due to a continuous increase in the number of the free cells which have only one nucleus. A few scattering multinuclear cells may also occasionally be observed. The lymphadenoid character is preserved in the newly formed tissue, but the distinctions between the cortical follicles and the reticulating medullary cords on the one hand, and the lymph-sinuses on the other hand, are lost; and the trabeculæ of the connective-tissue framework, as well as the capsule of the gland, become infiltrated with round cells. At the same time all trace of a germinal centre in the lymph-nodes ceases to be recognizable.

The cause of the development of lymphadenomata is unknown, and the whole formative process is difficult to explain. The alterations which take place in the structure of the gland are opposed to the view which regards this process as a simple hypertrophy. No definite proof has been brought forward in favor of an infective origin; in fact, no parasites have ever been demonstrated in these structures. So we are compelled to reckon the affection among the tumors.

It is of interest to note that in part of the cases the growth of adenoid tissue is associated with an increase of leucocytes in the blood; while in another portion of the cases only cachectic and anæmic conditions are established. Accordingly two separate processes are recognized—a *leucæmic lymphadenoma* or *adenia*, and a *pseudoleucæmic* or *simple adenia* (Hodgkin's disease).

The term **lymphosarcoma** is applied to a proliferative process originating in the *lymphadenoid tissue of the lymphatic glands, the spleen, the tonsils, and the mucous membrane of the pharynx, palate, stomach, and intestinal canal;* the new tissue thus developed exhibiting the characteristics of lymphadenoid tissue—that is to say, a reticulated framework which incloses cells of the character of lymphocytes. The distinction between lymphosarcoma and lymphadenoma rests, in the first place, on the fact that in the former, as the new growth of tissue progresses, it does not limit itself to the lymphadenoid organ, but breaks through into the neighboring structures; and, in the second place, on the further fact that, in the former, metastases occur either by way of the lymph-channels or by that of the blood-vessels, according to whichever of the two gives way and permits the entrance of portions of the new growth.

The new growths due to proliferative processes going on in the mucous membranes may form very large swellings, which break down and form ulcers. When the lymphatic glands undergo proliferation, a large mass of conglomerated nodules consisting of lymph-glands may be formed. Here, too, we may have necrosis as a result of obliteration of the vessels.

The etiology of lymphosarcoma is unknown; it may be looked upon as a particular form of sarcoma (cf. § 123).

It is impossible to draw the line sharply between lymphosarcoma and lymphadenoma; in fact, the former may develop from the latter.

According to their structure we can differentiate hard and soft forms of lymphosarcoma, the latter being characterized by a stronger development of the reticulum, often also by the formation of fibrous connective tissue.

Enlarged lymphatic glands are often called **lymphomata**, this term being applied to entirely different affections of the glands; therefore to lymphadenoma, to lymphosarcoma, and also to those enlargements which are caused by infection with the bacilli of tuberculosis or of typhoid fever, or with the virus of syphilis. If the use of this term is insisted upon, it should always be accompanied by a word which indicates what kind of lymphoma is meant. Lymphadenoma and lymphosarcoma are commonly called malignant lymphoma.

(*l*) *Sarcoma.*

§ 122. A **sarcoma** is a *connective-tissue tumor in which the cellular elements are much more prominent than the intercellular substance, not only on account of their number, but often also by reason of their size.* The sarcomata are therefore closely related to undeveloped connective tissue, and a comparison between sarcoma and embryonic tissue is by no means far-fetched.

Sarcomata always develop in one of the tissues belonging to the group of connective substances—that is to say, in formed or unformed connective tissue, in cartilage, in bone, in mucous tissue, in a lymphatic gland, or in adipose tissue. The transformation into tumor-tissue takes place by growth and multiplication of the existing cells. The cells usually divide by mitosis, and the faster the tumor grows the more numerous are the mitoses. Besides the typical mitoses there are atypical forms of all sorts; sometimes also nuclei broken into fragments.

When fully developed, sarcomata form tumors which are separated from the surrounding tissues by more or less sharply defined limits. They may grow in any part of the body where there is connective tissue, but they are found in certain regions far more frequently than in others. For example, they are found much oftener in the skin, fasciæ, intermuscular connective tissue, bone, periosteum, brain, and ovaries than in the liver, lungs, intestine, and uterus.

The development and form of the cells vary considerably in different sarcomata. The intercellular substance is sometimes scanty, soft, or even like tough mucus; at other times it is more abundant, and resembles in character rather the basic structure of the developed normal connective substances.

The amount of the intercellular substance has a marked influence upon the consistence and color of the tumors. The **medullary variety** presents a marrow-white or grayish-white cut surface, and is rich in cells and poor in intercellular substance. A hard and dense tumor is poorer in cells and richer in fibrous intercellular tissue. Such tumors shade by insensible gradations into fibromata. Varieties upon the border-line are called **fibrosarcomata.** The cut surface of a sarcoma presents throughout pretty nearly the same appearance, unless retrograde changes or an unequal distribution of blood-vessels cause differences. It is usually uniformly smooth and of a milk-white color in the medullary forms, or clear grayish white and somewhat translucent, or of a bright grayish red or grayish brown, in the firmer varieties. The hard varieties are of a brilliant-white or yellowish-white color.

The development of blood-vessels varies in sarcomata. Sometimes the vessels are remarkably numerous and broad—in fact, ectatic (*telangiectatic sarcomata*). Usually the vessels have walls easily distinguishable from the tumor-substance, but the tumor-cells themselves may also constitute the outer cells of the walls of the vessels; and in such a case the cells of the walls of the vessels also take part in the growth of the tumor. Lymph-vessels have not been demonstrated in sarcomata.

Retrograde changes—such as fatty degeneration, mucoid degeneration, liquefaction, cheesy degeneration, necrosis, hæmorrhage, gangrene, ulceration, etc.—are common occurrences in sarcomata.

Sarcomatous tumors may be divided into three classes. The first of these includes the *simple sarcomata*—sarcomata in the narrower sense, that is, tumors which are formed according to the type of fœtal connective tissue, and which show, therefore, a more or less even distribution of the cells, without any formation of separated foci or groups of cells. The second class includes those sarcomata which show *a particular arrangement and grouping of the individual elements*, so that in appearance they resemble the epithelial tumors. The third class is characterized by *secondary changes in the cells, the intercellular substance, and the blood-vessels*, which give to the tumor a peculiar appearance.

The *etiology of sarcomata* is not a simple one. They occur oftener in youth than in old age. Some develop in fœtal life and owe their origin to some local malformation. Sometimes they develop as the result of a trauma. A parasitic origin has not been demonstrated. Usually there is a single primary tumor; but multiple primary sarcomata are sometimes observed, as, for example, in the skin and in the bone-marrow. The softer tumors lead to metastases.

§ 123. **Simple sarcomata** include both the soft medullary forms and those of a firmer consistency, which shade off insensibly into the fibro-sarcomata and the fibromata. Among these forms several subordinate varieties may be distinguished, according to the character of the cells.

Small round-celled sarcomata are very soft, rapidly growing tumors, which develop especially in the connective tissue of the limbs and supporting framework of the body, and also in the skin, testicles, ovaries, and lymphatic glands. The cut surface of a section of one of these growths appears milky white, and sometimes shows caseous or softened areas. If scraped the surface yields a milky fluid. The structure is very simple. The tumor is composed almost wholly of round cells and vessels (Fig. 220). The cells are small and frail; they have very little protoplasm, and a spherical or slightly oval, rather large and bladder-like nucleus (*e*), which seems to be more highly developed than the nuclei in lymphatic elements.

Between the cells lies a very scanty amount of granular and delicately fibrillated intercellular substance. The vessels traverse the masses of cells in the form of very thin-walled canals. If the tumor be examined at its very margin of growth among the muscular fibres, its tissue will be found to present an aggregation of round cells (Fig. 220, *b*, *c*) in the connective tissue lying between the muscles. Often in close proximity to the cells of the tumor there are lymphatic elements whose nuclei (*d*) stain more deeply than those of the tumor itself.

Fig. 220.

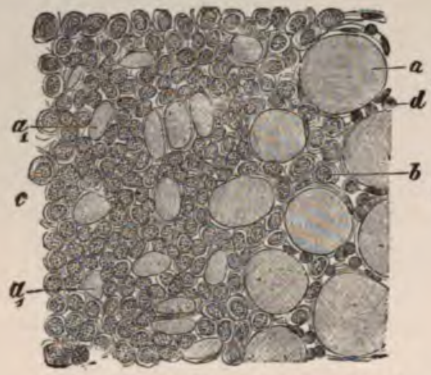


Fig. 221.

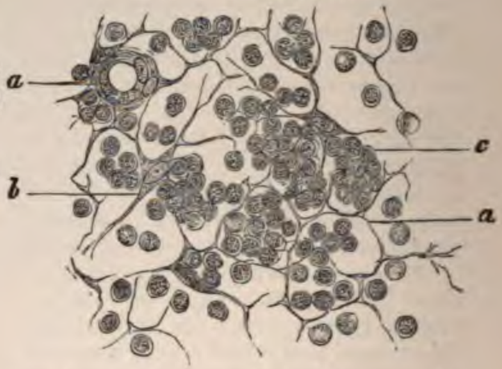


FIG. 220.—Section through the margin of a sarcoma of the intermuscular connective tissue of the neck. *a*, Normal muscle cut transversely; a_1, Atrophied muscle cut transversely; *b*, Round cells of the sarcoma growing between the muscle-fibres; *c*, Mature tumor-tissue; *d*, Round cells of the character of white blood-corpuscles. (Carmine preparation. Magnified 300 diameters.)

FIG. 221.—Section from a lymphosarcoma of the mucous membrane of the nose, after shaking it about in water to free it from the greater number of its cells. *a*, Reticulum; *b*, Cells of the reticulum; *c*, Round cells; *d*, Blood-vessel with actively growing cells. (Carmine preparation. Magnified 300 diameters.)

A second form of round-celled sarcoma is called **lymphosarcoma.** This tumor imitates in structure the lymphatic glands, at least to this extent: that the stroma, which holds together large numbers of round cells, is composed of a vascular reticulum (Fig. 221, *a*), a part of which, at least, is made up of branching and anastomosing cells (*b*). These relations are easily made clear by shaking a section in a test-tube.

Macroscopically the tumor has the same appearance as other small round-celled sarcomata, and is as malignant as they are, both by reason of its rapid growth and by reason of the fact that it forms metastases.

Lymphosarcomata occur most frequently in the lymphatic glands or the lymphadenoid tissue of the mucous membranes, but they are also found in other situations (cf. § 121).

Large round-celled sarcomata occur in the same localities where the small round-celled sarcomata are found, but their cells are much larger than those of the latter. These two forms of tumors resemble each other closely, although the large-celled variety is not so soft as the small-celled. The cells are richly supplied with protoplasm, and possess large bladder-like oval nuclei (Fig. 222). Many of the cells have two nuclei, some more than two. Between the cells is a reticulated intercellular substance (Fig. 222), in which both spindle-shaped and branching cells unite to form an alveolar network in whose meshes the large round epithelioid cells lie. For this reason such tumors have been called *large round-celled alveolar sarcomata* (Billroth). The vessels are for the most part thin-walled.

In certain forms of large round-celled sarcomata the cells are of varying size (Fig. 223), and among them are many long or irregularly shaped cells, so that the tumor may well be called a **sarcoma with polymorphous cells.** The nuclei, too, vary much in size (Fig. 223) in these tumors, and there may be a large number of them in a single cell (*e*) (multinucleated giant cells).

Fig. 222.

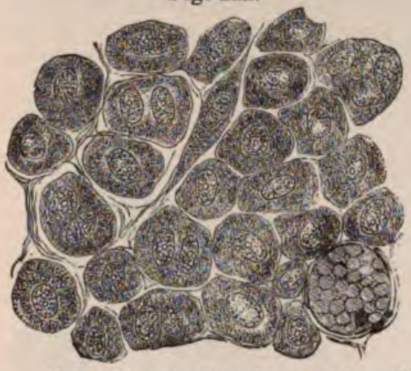


Fig. 223.

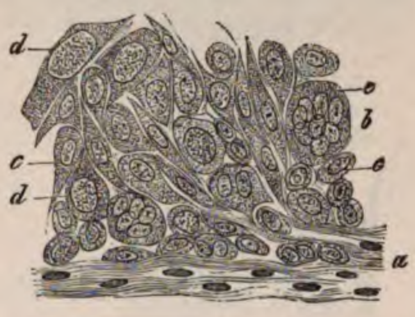


FIG. 222.—Section from a fungoid large round-celled sarcoma of the skin of the leg. (Carmine preparation. Magnified 400 diameters.)

FIG. 223.—Section of a sarcoma of the breast, with variously shaped cells. *a*, Connective tissue; *b*, Sarcomatous tissue; *c*, Smaller cells; *d*, Cells with hypertrophic nuclei; *e*, Multinuclear cells. (Preparation stained with Bismarck brown. Magnified 300 diameters.)

The large round-celled sarcomata and the sarcomata with polymorphous cells are in general not so malignant as the small round-celled ones; but nevertheless they do give rise to metastases.

Spindle-celled sarcomata are among the commonest of tumors. They are usually much denser than the round-celled varieties, but they may also be of a soft *medullary character*. A cut section usually appears grayish or yellowish white and somewhat translucent, or it may present a more or less reddish hue, by reason of its vascularity. Medullary tumors whose cells have undergone fatty degeneration may have a pure-white color. In general these tumors are much less malignant than the round-celled ones, but their character in this respect varies according to their location and their richness in cells.

According as the cells are large or small, we may distinguish **large spindle-celled and small spindle-celled sarcomata.** By teasing small bits of the tumor-tissue some of the cells may be isolated, and in this way very long spindles may occasionally be obtained (Fig. 224). The cells lie side by side, arranged in bundles, which in a section may be cut transversely or obliquely or longitudinally—a proof that they are interwoven in different directions.

This arrangement of the spindle-cells in bundles is often very striking. In other cases it is entirely absent, and for considerable distances the spindles will be found to lie in the same direction. Sometimes the direction of the spindles is determined by the direction of the blood-vessels—i.e., the individual bundles build each a sheath about its own blood-vessel.

Between the spindle-cells there may be a very little intercellular substance, or it may not be possible in the section to demonstrate any intercellular substance. In other cases it is more abundant and of a fibrillary character. In such cases the cells have less protoplasm, so that often it is scarcely possible to demonstrate any protoplasm around the nucleus, and the processes at the poles of the cell seem to spring directly from the nucleus (nuclear fibres). Such varieties are dense and hard. They form the connecting-link between sarcomata and fibromata, and are called **fibrosarcomata.**

Fig. 224.

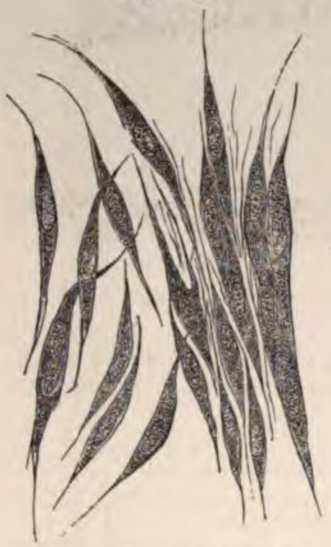


Fig. 225.

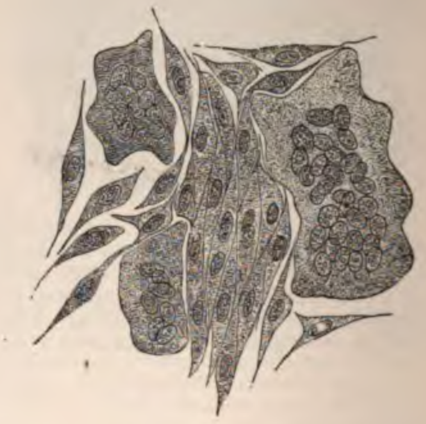


FIG. 224.—Spindle-cells from a large spindle-celled sarcoma of the cheek. (Teased preparation. Magnified 400 diameters.)

FIG. 225.—Cells from a medullary giant-celled sarcoma of the tibia. (Preparation stained with hæmatoxylin. Magnified 400 diameters.)

Sarcomata with polymorphous cells are also found among the spindle-celled sarcomata. They contain spindle-shaped, triangular, and prismatic cells, and also star-shaped cells and cells which are quite irregular in shape (Fig. 225). Each cell has the shape which fits most perfectly into the space allotted to it.

Both in polymorphous-celled and in spindle-celled sarcomata are found more or less numerous giant cells (Figs. 223 and 225), so that the name of **giant-celled sarcoma** may properly be applied to these tumors. They develop most often from some part of the osseous system, but they are found in other parts of the body also (Fig. 223).

§ 124. **Sarcomata which present an organoid structure** are usually found among those forms called **alveolar sarcomata** and **tubular sarcomata.** These growths are connective-tissue tumors in which the cells, especially the larger ones, are arranged in groups, so that it is possible to distinguish a *vascular stroma* and *separate aggregations of cells.*

In many cases the peculiar alveolar and tubular structure of the tumor is a direct result of the particular locality from which it originates, the large tumor-cells springing from particular cells of the connective tissue. Sometimes the large epithelioid tumor-cells plainly result from a *proliferation of endothelial cells* (Fig. 226, *d*, *e*), and hence these tumors have been called also **endotheliomata.** If it can be demonstrated that they arise from the endothelium of the lymph-vessels, many authors apply the name *angiosarcoma*, or, more correctly, *lymphangiosarcoma*, to them. Such tumors occur in the serous membranes of the large cavities of the body, and in the membranes of the central nervous system, partly as limited and well-defined, partly as ill-defined and flat swellings. Where the delicate membranes of the brain are involved, it is perfectly evident that the elements which contribute to the formation of the tumor are the endothelial cells, which clothe the connective-tissue trabeculæ, and which swell up and multiply, so that in the subarachnoid tissue, and in the pia (Fig. 226, *d*, *e*), formations are produced which remind one of ducts and alveoli of glands, or even of solid club-shaped and racemose gland-structures—formations which present a strong resemblance to what is observed in adenomata and carcinomata. If the growth extends to the pial con-

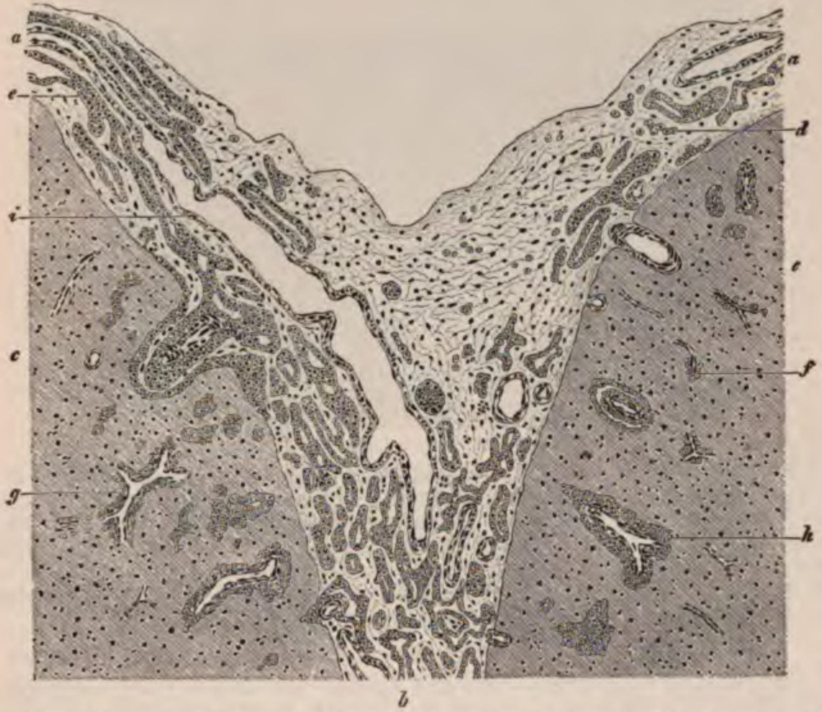


FIG. 226.—Section through an endothelioma of the pia mater and cerebral cortex, diffusely spread out over the surface of the brain and spinal cord. *a*, Pia mater on the surface, *b*, in a sulcus, of the brain; *c*, Cortex; *d*, *e*, Endothelial growths in the subarachnoid spaces; *f*, *g*, *h*, Endothelial growths in the pial sheaths of the cortical vessels; *i*, Longitudinal section through a vein. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 30 diameters.)

nective-tissue sheaths which envelop the vessels of the cortex, we may have also, in these new localities, bands and nests of large epithelioid cells (Fig. 226, *f*, *g*, *h*).

In a similar manner the endothelial cells of the dural lymph-vessels may take on a proliferative activity and convert the lymph-vessels into gland-like canals or even into solid cords of cells (Fig. 227, *c*, *d*), thus producing a peculiarly constructed endothelioma, one having considerable resemblance to a tubular carcinoma. The endotheliomata of the pleura, peritoneum, and mamma show nearly the same structure.

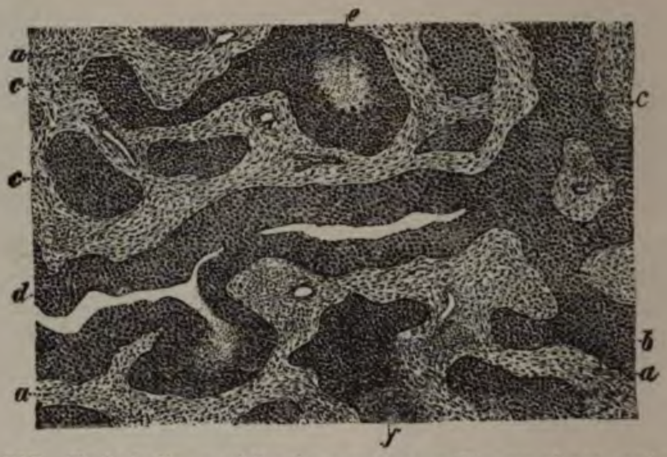


FIG. 227.—Endothelioma of the dura mater. *a*, Stroma of connective tissue; *b*, An aggregation of small round cells; *c*, Nests and cords of cells, resulting from the proliferation of the endothelium of the lymph-vessels; *d*, Cord of endothelial cells with a lumen; *e*, Area of fatty degeneration in a nest of endothelial cells; *f*, Cord of cells, gradually mixing with the bordering connective tissue on the right. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 25 diameters.)

In a second class of alveolar and tubular sarcomata the growth proceeds from the cells of the walls of the blood-vessels and neighboring tissues. Accordingly the name **angiosarcoma** (Waldeyer, Kolaczek), or, more correctly, *hæmangiosarcoma*, has been given to them.

Even in endotheliomata of the pia mater the observation may be made that the proliferative processes in the region of the cerebral cortex are confined in large degree to the adventitia of the arteries (Fig. 226, *f*, *g*, *h*), thus leading to the production of cords of cells which completely surround the vessels. But there are also other forms of tumors in which this perivascular deposit of proliferating cells is characteristic of the tumor throughout its whole extent. The tissue of the tumor, in typical cases, is almost wholly composed of a tangle of vessels (Fig. 228, *a*, *a*) whose walls are surrounded by heavy masses of cells, which extend even as far as to the endothelium (*b*). Such a tumor, therefore, is made up essentially of thick-walled cellular tubes, which partly follow an independent course and partly unite with other tubes by anastomoses, thus giving rise to a complicated mass of twisted and interwoven cords of cells (*plexiform angiosarcoma*).

In a typically developed tumor of this kind the masses of cells show a cylindrical arrangement; but this arrangement may sometimes be disturbed. Thus, for example, two contiguous cords of cells may become merged into one, and some of the vessels may undergo obliteration. If the remaining vessels with their surrounding connective tissue form a network, or if the process of proliferation has filled out the spaces left between the walls of a capillary network, the fully developed tumor may present an alveolar structure. However, it should be mentioned here that in both endotheliomata and angiosarcomata the alveolar and the tubular structure may be wholly lost in places, through the diffuse manner in which the proliferation takes place.

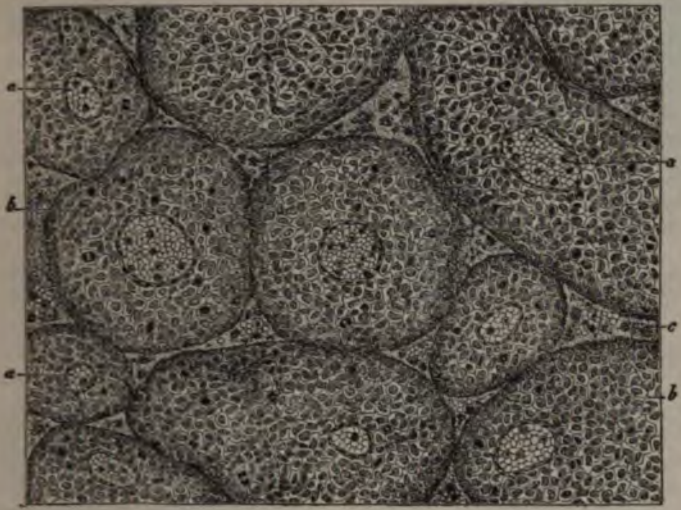


FIG. 228.—Section through a nodular angiosarcoma of the thyroid. *a, a*, Vessels in section; *b*, Perivascular cellular cylinder in cross-section, showing numerous mitoses; *c*, Granular masses with scattered cells between the cellular cylinders. (Preparation hardened in Flemming's mixture, stained with safranine, and mounted in Canada balsam. Magnified 80 diameters.)

Angiosarcoma occurs in the brain, kidney, testicle, lymphatic glands, breast, skin, bone, thyroid, and liver, although it is a very rare occurrence in the two situations last named.

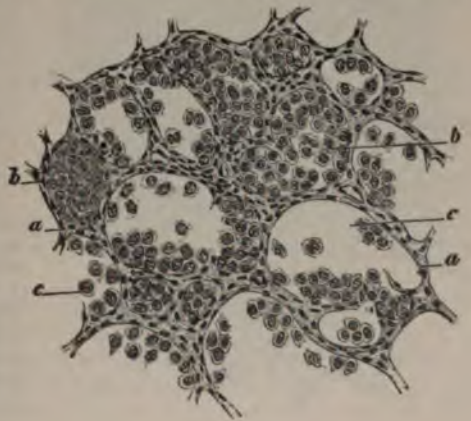


FIG. 229.—Section through an alveolar sarcoma of a lymphatic gland. *a*, Stroma; *b*, Nests of cells; *c*, Alveoli with cells lying free within them. (Preparation hardened in Müller's fluid, stained with alum carmine, and mounted in Canada balsam. Magnified 100 diameters.)

Alveolar sarcoma develops by no means rarely in fleshy warts or moles or birthmarks. In such formations there are, in the corium or in the papillæ, peculiar nests of large cells, which proliferate actively when a sarcoma begins to develop. As these nests of cells probably represent pathologically developed lymphatic vessels (cf. § 117, Fig. 211), these sarcomata may properly be reckoned among the endotheliomata. Moreover, alveolar sarcomata in which a connective-tissue vascular stroma (Fig. 229, *a*) incloses nests of large cells (*b*, *c*) are also observed in the bones, lymphatic glands (Fig. 229), and other organs.

The term *angiosarcoma* is not used with the same meaning by all authors. Waldeyer introduced the name for tumors springing from the adventitia of blood-vessels. Kolaczek has extended its use so that it shall include also those which spring from the lymph-vessels. It certainly is more correct, as well as more practical, to employ the name only for those tumors to which it was originally given, and to apply the name endothelioma to tumors starting from endothelium. If, however, the application of the term be insisted upon for both classes of tumors, the limiting adjective ought never to be omitted; the tumor then being designated either as a hæmangiosarcoma or as a lymphangiosarcoma.

§ 125. Among the **secondary changes** which a sarcoma may undergo, and which give to it a distinguishing peculiarity, the formation of pigment may be mentioned as the most important. This change, which characterizes the **melanosarcomata**, is oftenest observed in sarcomata of the skin and eyeball, and the tumors thus affected present a brown or black, or sometimes also a spotted appearance. Melanotic sarcomata are malignant tumors, which form metastases and often affect, by means of secondary nodules, many of the organs of the body, of the skin, and of the muscles. Sometimes the primary tumor is only faintly pigmented or pigmented in part, while the secondary nodules are almost black.

Pigmented sarcomata of the skin grow usually from moles and pigmented warts (cf. § 124), and usually belong, therefore, to the alveolar group of sarcomata (Fig. 230); but the alveolar structure is not always typical, being usually more or less obscured by an even distribution of the newly formed cells. The pigment which exists in yellow and brown granules or as a diffuse staining of certain cells (cf. § 73) lies often chiefly in the perivascular tissues (Fig. 230, *e*). There it is embedded in small connective-tissue cells. It may also be deposited in the large tumor-cells (*b*),

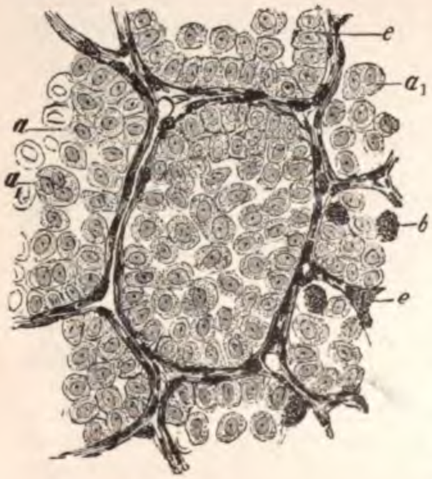


FIG. 230.—Section through a melanotic alveolar sarcoma of the skin. *a*, Sarcoma-cell of an epithelial character, containing one nucleus; a_1, The same, with more than one nucleus; *b*, Cells containing pigment; *e*, Stroma containing blood-vessels and pigment. (Preparation stained with hæmatoxylin. Magnified 300 diameters.)

and in different places may be found in almost all the different cells. If the pigmentation is very pronounced, the cells may degenerate and fall to pieces.

In certain rare cases tumors develop which present on fresh section a bright-green appearance, becoming dirty green on exposure to the light. To these tumors the name of **chloroma** has been given. According to the reports which have been published thus far, these tumors usually develop in the periosteum of the skull, and are made up of round cells lying in a reticulated stroma. They belong, therefore, to the round-celled sarcomata, and especially to the group designated lymphosarcoma. Von Recklinghausen classes this tumor with the lymphadenomata, of which he considers it a variety. According to Chiari and Huber, the green color is due to the presence in the cells of small shining spherules which give the microchemical reaction of fat. The disappearance of the color in alcohol lends support to this statement. On the other hand, von Recklinghausen claims that the color is parenchymatous.

A further peculiarity of sarcomatous as well as fibromatous and myxomatous tumors is the possible formation, within the tumor, of circumscribed areas of calcification, which resemble the sand-like particles found in the brain; and from this circumstance some authorities have felt warranted in calling such tumors **psammomata** (*acervulomata, sand-tumors*). They are found chiefly in the membranes of the central nervous system and in the pineal gland, where they form nodular tumors; and if these concretions are present in sufficient numbers, their existence may readily be made out, even with the naked eye, through their white color and through the resistance encountered by the knife when a section is made.

The lime concretions form either round bodies with concentric layers (Fig. 231, *a, b, c*), as they occur normally in the plexus in the form of brain-sand; or they are more lanceolate (*d*) or nodular (*e*). As has been already mentioned in § 70, the basic substance of the concretions is formed partly of connective tissue which has undergone hyaline degeneration (*d, e*), partly of degenerated cells (*a, b, c*).

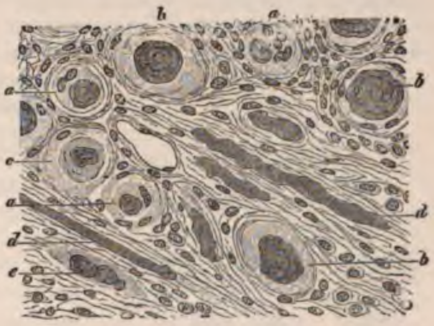


FIG. 231.—Section of a psammoma of the dura mater. *a*, Hyaline nucleated globule including a concretion; *b*, Concretion with non-nucleated hyaline border, lying in fibrous tissue; *c*, Concretion with hyaline border; *d*, Lanceolate concretion in connective tissue; *e*, Lanceolate formation containing three concretions. (Preparation hardened in alcohol, decalcified in picric acid, and stained with hæmatoxylin and eosin. Magnified 200 diameters.)

Sometimes deposits of lime take place in the basic substance of cellular sarcomata of bone (Fig. 232, *c, d*), giving rise to a hardening of the tumor similar in appearance to ossification. As the hardened portions consist purely of calcified connective tissue, and lack entirely the structure of bone, these tumors must not be reckoned with osteosarcomata.

The better plan is to give them the name of **petrifying sarcoma** (*sarcoma petrificans*).

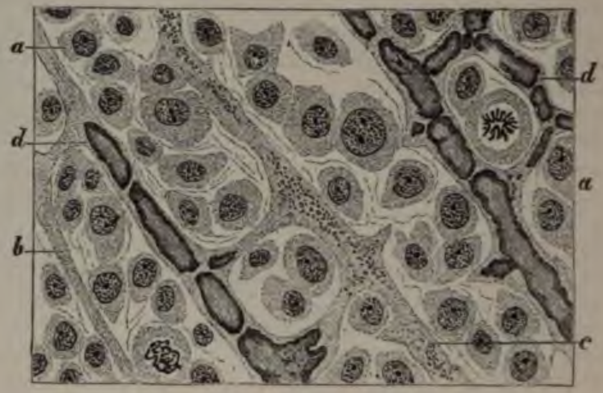


FIG. 232.—Petrifying large-celled sarcoma of the tibia. *a*, Polymorphous tumor-cells; *b*, Alveolar stroma; *c*, Trabeculæ of the stroma with small calcareous concretions; *d*, Petrified bands of the stroma. (Preparation hardened in Müller's fluid and alcohol, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 365 diameters.)

§ 126. Finally, there are certain sarcomata which are characterized by the **mucoid** or **hyaline degeneration** of a portion of the tumor. If, as a result of this, peculiar bands of cells, aggregations of cells interrupted here and there by clear hyaline spaces, and hyaline masses in elongated or branching forms are developed, the tumors in which such changes take place are by many authorities called **cylindromata**—a name which has also been given to cancers in which similar hyaline alterations occur.

Sometimes even the ordinary soft, cellular forms of sarcoma present a more than usually translucent appearance, and a cut surface which yields a mucous or somewhat cloudy fluid. This condition is due to the existence of a mucoid degeneration, which may be recognized by the swollen state of the cells, as well as by the formation of drops in their interior. In hardened preparations this mucoid degeneration can no longer be made out easily. The cells are shrunken (Fig. 233, *b*), and separated from the stroma (*a*) by a clear zone. Sometimes one may come across a few nuclei which are much swollen (*c*) and quite bright, but their surrounding protoplasm will be found to have wholly disappeared through mucoid degeneration.

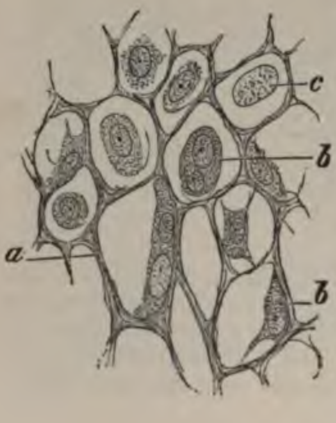


FIG. 233.—Sarcoma myxomatodes. *a*, Stroma; *b*, Sarcoma-cells separated from the stroma by a clear area (partly the result of shrinkage in chromic acid and alcohol); *c*, Swollen nucleus without protoplasm. (Preparation stained in hæmatoxylin. Magnified 400 diameters.)

Sometimes this mucoid degeneration is evenly distributed throughout the parenchyma of the tumor; in other cases it occurs in patches, so that degenerated areas alternate with others which are still in a healthy condition. Frequently this form of degeneration gives rise to *hyaline balls* and *branching hyaline figures*, between which the cells which have escaped appear in bands that present a multitude of shapes.

Those tumors which appear in section, even to the naked eye, as partly hyaline and partly grayish white sometimes present a peculiar *combination of sarcomatous and myxomatous tissue*. The latter consists of a mucoid groundwork and a network of anastomosing cells (Fig. 234, *a*). The sarcomatous portion, on the other hand, is made up of branching columns and rows of cells pressed close together (*b*), which often anastomose and give the tumor a peculiar appearance.

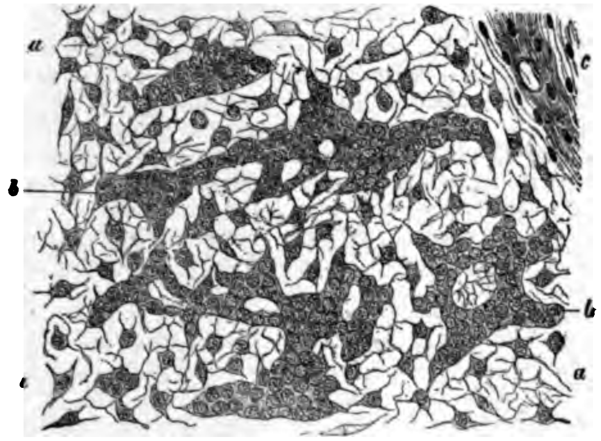


FIG. 234.—Section through a myxosarcoma (cylindroma). a, Mucous tissue; *b*, Strings of cells; *c*, Fibrous tissue. (Preparation stained with carmine and mounted in glycerin. Magnified 250 diameters.)

From their mode of construction such tumors must be called *myxosarcomata*. The anatomical reason for the existence of the plugs and cords of cells is not always discoverable. There is no apparent connection with the distribution of the blood-vessels, for these run at times in the very directions in which the cords of cells are absent (Fig. 234, *c*). According to von Recklinghausen, the cords of cells may lie in lymph-vessels and lymph-spaces, while the connective tissue which intervenes presents a wholly homogeneous aspect.

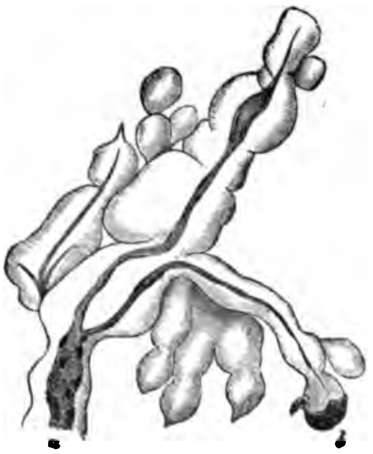


FIG. 235.—Cluster of blood-vessels having hyaline sheaths and hyaline processes; from a cylindroma. *a*, Small blood-vessel; *b*, Layer of cells resembling epithelium, upon a hyaline bulb-like process. (From Sattler. Magnified 200 diameters.)

Hyaline degeneration occurs relatively often in *angiosarcomata*, and in these growths the connective tissue and blood-vessels, as well as the perivascular masses of cells, may in part be transformed into a hyaline substance (Fig. 235); as a result of which the tissue is made up of multiform cords and masses of cells, and hyaline masses in which few or no cells are to be found.

A part of the cylindromata are therefore to be reckoned among the angiosarcomata, of which they form a group that is characterized by hyaline degeneration.

(*m*) *Mixed Forms of the Connective-tissue Tumors.*

§ 127. Various combinations of different sorts of tissue-formations have been described in the preceding paragraphs. Speaking literally, there are no tumors which are composed of a single kind of tissue. In the first place, in every tumor of any size there is a new formation of blood-vessels, and those tumors, such as chondroma, osteoma, sarcoma, myoma, and myxoma, which are not made up of connective tissue have nevertheless a certain amount of it in their structure.

The reason why such tumors are not spoken of as mixed tumors is because in them one kind of tissue is insignificant when compared with the other, and also because it exists to a certain degree only for the benefit of the other. When this relation is changed, so that the lesser tissue forms an integral part of the tumor, and its presence affects the character of the tumor, then the name **mixed tumor** is applied, and the name of one kind of tissue is made an adjective to qualify the other, or from the names of the two tissues a compound name is formed. If, for example, the vessels are very abundant and at the same time large or cavernous, as often happens in a glioma or a fibroma, the tumor is spoken of as a glioma or a fibroma—as the case may be—telangiectodes or cavernosum. If fatty and mucous tissues coexist, the tumor is called a lipoma myxomatodes or a lipomyxoma. Finally, a combination of cartilage and sarcoma is called a chondrosarcoma.

Combinations of cartilaginous and mucous tissues, or *of cartilaginous and sarcomatous tissues*, occur frequently in the parotid (Fig. 236). Most of the tumors which develop in this region are *chondromyxomata* or *chondrosarcomata* or *chondromyxosarcomata*. Tumors of the fasciæ or of the intermuscular connective tissue are often

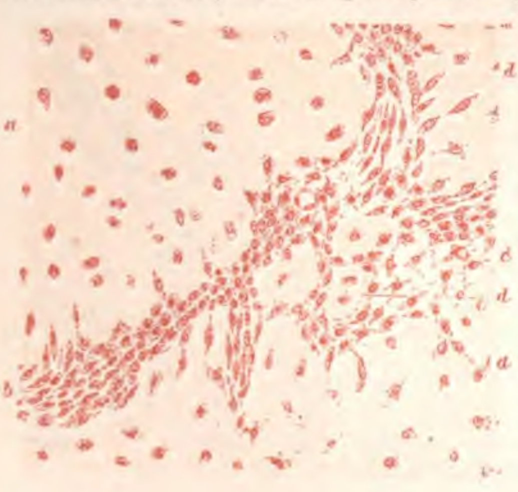


FIG. 236.—Chondromyxosarcoma of the parotid. *a*, Cartilage-tissue; *b*, Sarcoma-tissue; *c*, Mucous tissue; *d*, Cartilage in process of degeneration and change into sarcomatous and mucous tissue. (Preparation hardened in alcohol, stained with carmine, and mounted in Canada balsam. Magnified 80 diameters.)

made up of *connective tissue*, *sarcomatous tissue*, *mucous tissue*, and *adipose tissue*; and, in addition, the tumor is often of a telangiectatic character. Such a composite growth may be due to the fact that from the outset the tumor develops along different lines; or, in other cases, the connective tissues, after undergoing certain secondary changes, may pass from one form to another in the same group. Thus, for example, in *chondrosarcomata* of the parotid gland, the sarcomatous tissue or the mucous tissue is wont to traverse the cartilaginous tissue in cords or bands (Fig. 236, *b*); and in some places the cartilage changes directly, in other places gradually, into mucous tissue (*c*) or into sarcomatous tissue (*b*); and where this takes place the groundwork of the cartilage gradually disappears (*d*) and is replaced by a mucoid groundwork containing proliferating spindle-shaped and star-shaped cells.

Combinations in which there is development of bone occur in those tumors which spring from bone. There are two forms of tumors in which such a formation of bone occurs, namely, the *osteochondroma*—i.e., a union of bony and cartilaginous tissues—and the *osteosarcoma* or *osteofibroma*—a union of osseous and sarcomatous or fibrous tissues.

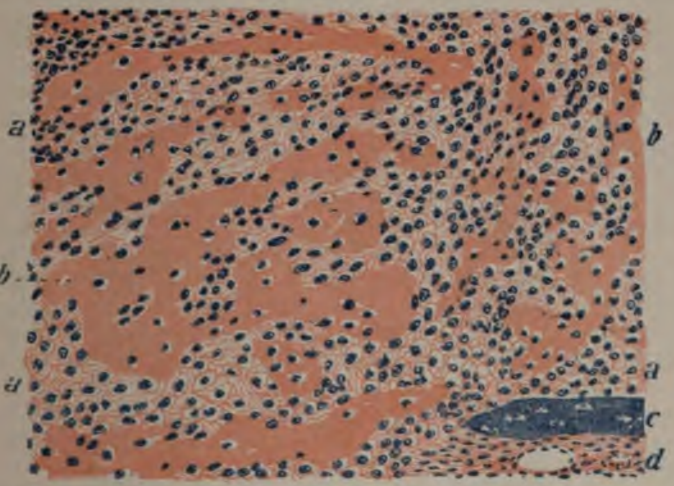


FIG. 237.—Osteoid sarcoma of the ethmoid bone. *a*, Sarcoma-tissue; *b*, Osteoid tissue; *c*, Plate of old bone; *d*, Vascular fibrous tissue. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 45 diameters.)

The *osteosarcoma* and the *osteofibroma* may arise from any bone in the body; they develop usually from the periosteum. A characteristic feature of these tumors consists in the formation of bony trabeculæ by means of condensation changes in the basic substance (Fig. 237). The new-formed bony groundwork may calcify immediately upon its formation, so that the tumor becomes permeated with hard bony trabeculæ. But it occasionally happens that the calcification fails to take place (Fig. 237, *b*), while the trabeculæ still preserve the characteristics of osteoid tissue; in which case it is perfectly proper to give to the growth the name of *osteoid sarcoma*.

The *osteochondroma* is a hard tumor and is usually found in connection with the long bones; either growing out from some one portion of the bone or developing all around it as if the latter were a shaft piercing it. The starting-point for the development of these tumors is especially the periosteum, but the bone-marrow may also take part in the formation of cartilage and bone. Except in parts where pure cartilage may exist, it is not possible to cut through one of these tumors when fully developed, and they often grow to considerable size. When it is sawed through, the surface may be very like a sawed surface of solid bone. Only by careful observation can one distinguish the white bony substance from the more translucent cartilage. If the new growth has taken place at the same time in marrow and periosteum there will be found in the latter situation a cartilaginous tissue (Fig. 238, *g*) thickly traversed by trabeculæ of bone (*h*), arranged for the most part at right angles to the surface of the old bone, but also united in many places by transverse offshoots. The cartilage also contains little clefts and canals which hold the scanty blood-vessels and a little connective tissue. In the cortical layer of the bone (*a*) are seen a greater or less number of Haversian canals, dilated and filled with cartilage (*e*) even to the smallest cleft and to every canal which harbors a blood vessel, while this cartilage itself is

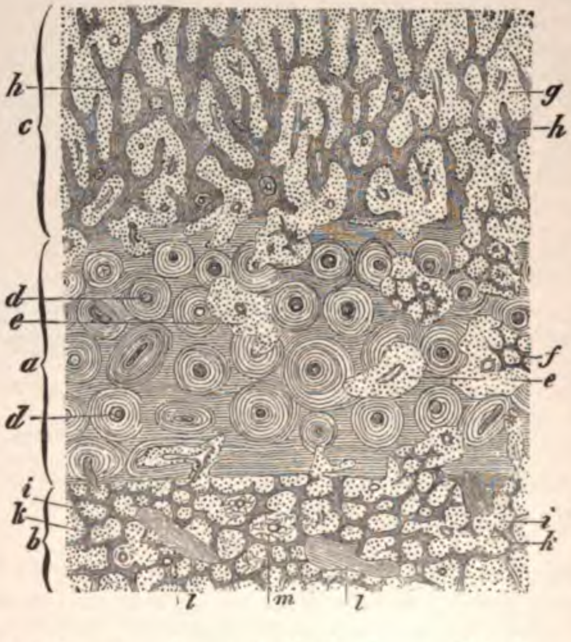


FIG. 238.—Section through an osteoid chondroma of the humerus. *a*, Cortical layer of the humerus; *b*, Medullary cavity; *c*, Periosteal new growth; *d*, Normal Haversian canals; *e*, Dilated Haversian canals filled with cartilage containing at *f* new-formed bone; *g*, Cartilage formed from periosteum containing bone-trabeculæ, *h*; *i*, Cartilage formed from the marrow-tissue with new-formed bone-trabeculæ, *k*; *l*, Old bone-trabeculæ; *m*, Remains of medullary tissue. (Magnified with a hand magnifying-glass. Preparation decalcified with picric acid and double-stained with hæmatoxylin and carmine.)

traversed in places in its central portions with new-formed bone-trabeculæ (*f*). In the place of the fat-containing bone-marrow (*b*) is found a vascular cartilage which also contains numerous little trabeculæ of bone (*k*).

If an active growth of sarcoma-tissue takes place in an osteochondroma, as may happen in its outer layers, there will be developed an *osteochondrosarcoma.*

2. *Tumors whose Structure Comprises Epithelium as well as Connective Tissue and Blood-vessels.—Epithelial Tumors.*

(*a*) *Preliminary Remarks.*

§ 128. In the case of the tumors described in the last chapters, we had to do with those new growths which arise from some tissue of the connective-tissue group—a tissue, therefore, which came from the middle germ-layer. In the development of the tumors which are to be described in the following paragraphs the epithelia—that is, the derivatives of the upper and lower germ-layers—are also directly involved. In fact, it is the very tissue which is formed from these layers which gives to these tumors their special character. They are therefore properly included under the general term of **epithelial new growths.**

All the tumors belonging to this category consist in part of epithelial cells, in part of vascular connective tissue. The latter forms the stroma —the framework which gives shelter and support to the epithelial elements. The pattern upon which these tumors are constructed is to be found in the various glandular organs, whose different stages of development are in many particulars mimicked by the tumors. To a large extent, therefore, they resemble the various glandular organs of the body; but the degree of this resemblance varies greatly in different tumors, and on this ground we may make a division into two great classes.

The first of these classes comprises the **adenomata**—that is, tumors which imitate with a certain degree of perfection any one of the normal gland types. The tumors of the second class—the **carcinomata**—do not ordinarily reach any such perfection of imitation, or at least not throughout the whole new growth. Usually only the first stage of gland-formation is followed—the mutual ingrowing of epithelium and connective tissue—and this process is repeated over and over again. In this way—that is, by the multiplication of epithelial cells—cell-nests and plugs and cords of cells are formed, and these are continually being sheathed about by the growing connective tissue. The result of the process is a neoplasm whose connective-tissue stroma incloses multiform spaces filled with epithelial cells. These epithelial cells, however, do not arrange themselves in a layer along the wall of the space, as in an adenoma, nor do they leave any free space—a lumen—between themselves; but they are packed together as solid, irregularly arranged cell-masses.

The **epithelial cystomata** must be mentioned as an especial variety of the epithelial tumors. They are characterized by the formation of large spaces which are lined with epithelium and filled with fluid.

Carcinomata are malignant tumors which grow into the neighboring tissues, sooner or later penetrating into the lymph- and blood-vessels, and forming metastases. It must be remarked, however, that the malignancy varies according to the location of the carcinomata. They usually appear singly, but sometimes two carcinomata of the same variety, or two of different varieties, develop at the same time in the same individual.

Adenomata and cystomata are usually benign tumors, but there are examples of adenoma, as well as of cystoma, which, not only in structure, but also in method of growth, approach very closely to the carcinomata. They are doubtless transition forms between adenomata or cystomata on the one hand, and carcinomata on the other; and consequently a sharp boundary-line between adenoma and cystoma on the one hand, and carcinoma on the other, cannot be drawn. Moreover, an adenoma or a cystoma originally benign may in its growth assume the characteristics of a carcinoma. The development of this character of malignancy announces itself chiefly by the fact that the tumor breaks into the surrounding tissues. At the same time there is often noticed a more active and likewise a more atypical growth of epithelial cells.

The definition of the terms adenoma and carcinoma, just given, is founded on the anatomy and histogenesis of these tumors; and I maintain that this is the only rational definition which the anatomist can accept. Inasmuch, also, as tumors which arise solely from cells belonging to the middle germ-layer may correspond exactly to other tumors in whose formation epithelial cells certainly take a part, and even constitute the characteristic part of the growth, any definition which rests solely on an anatomical basis must necessarily be unsatisfactory. The definition of carcinoma as a tumor of alveolar type, in which a connective-tissue stroma contains cells in the form of nests, makes it impossible to draw any line of distinction between alveolar sarcomata and carcinomata. This purely anatomical definition of carcinoma has brought us to the point where the question is widely discussed whether a carcinoma arises only from epithelial structures, or whether it may not come also from connective tissue. Such a discussion becomes at once fruitless if the histogenesis of these tumors is accepted as a basis of classification. As a result of such a method of classification, only those tumors merit the name of carcinoma in which epithelial cells take an active part in the growth in the manner described above, while the connective-tissue tumors, which are anatomically similar but genetically very different, are called *alveolar sarcomata*.

(*b*) *The Adenomata and their Relations to Glandular Hypertrophies and Carcinomata.*

§ 129. The **well-defined adenomata** are benign tumors which spring from glands, and usually present the aspect of nodular tumors sharply separated from the surrounding tissues. They may develop in the large glands—as, for example, the liver, kidneys, and breast—or in the small glands—like the sweat-glands, for example. On the whole, they are by no means common, certainly not if the adenocarcinomata (§ 130) and the adenocystomata (§§ 136 and 137) are separated from them and classified by themselves.

The new growth consists of a tissue which in its structure closely resembles a normal gland (Figs. 239 and 240), but yet differs from it in the following respects: it does not reproduce all the anatomical characteristics of the fully developed gland, nor does it possess the power to perform the functions of the gland which it imitates.

Adenomata may be divided into two groups according to their histological construction—that is, according to whether they are patterned upon the type of a tubular gland or upon that of a racemose or alveolar gland. Upon this basis we may recognize an **alveolar adenoma** (Fig. 239) and a **tubular adenoma** (Fig. 240). Either of these forms may develop into an **adenoma papilliferum** by a more active growth of the epithelium and by the formation of connective-tissue papillæ which rise up

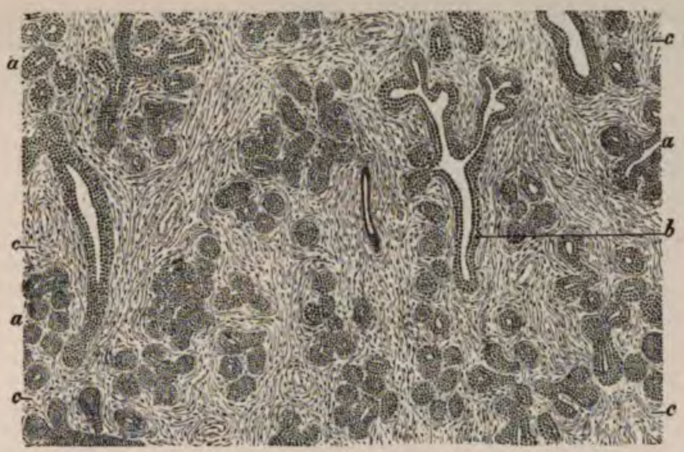


FIG. 239.—Alveolar adenoma of the breast. *a*, Terminal alveoli of gland; *b*, Ducts of gland; *c*, Connective-tissue stroma. (Preparation hardened in Müller's fluid and alcohol, stained in alum carmine, and mounted in Canada balsam. Magnified 30 diameters.)

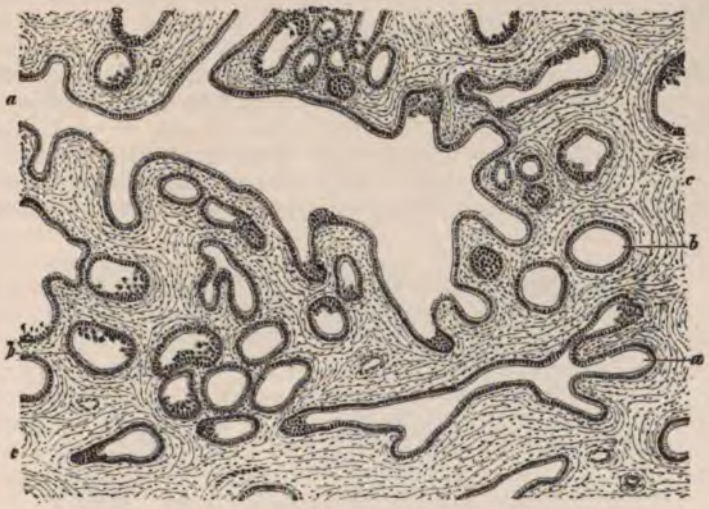


FIG. 240.—Tubular adenoma of the breast. *a*, Branching and dilated glandular ducts, cut longitudinally; *b*, The same, cut transversely; *c*, Stroma. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 30 diameters.)

from the inner surface of the walls of the tubes and alveoli of the gland (Fig. 241, *c*).

The development of an adenoma begins with the proliferation of the epithelium of the gland, and is speedily followed by the formation of glandular sprouts. The surrounding connective tissue, under these circumstances, is penetrated by these new-formed glands, and may itself also take on a more or less decided proliferative activity, which results in the formation of new tissue. In fully formed adenomata the connective-tissue stroma may be either well developed (Fig. 239, *c*, and Fig. 240, *c*) or only poorly developed (Fig. 241).

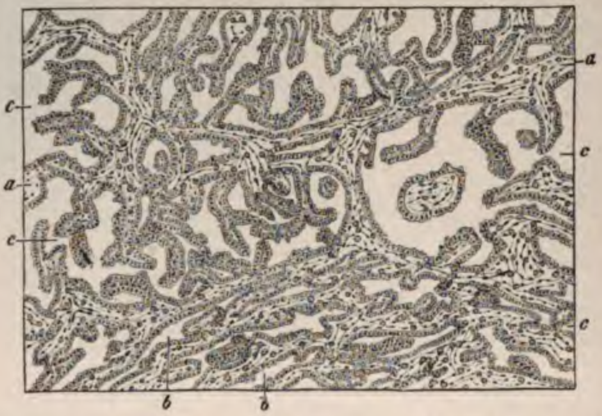


FIG. 241.—Adenoma tubulare papilliferum of the kidney. *a*, Connective-tissue stroma; *b*, Glandular tubules with diverticula; *c*, Tubules with markedly developed papillary excrescences. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 30 diameters.)

Adenomata occur in the breast in the form of nodular tumors, which vary in size from that of a hazel-nut to that of a man's fist; sometimes they are even larger. On section they appear to be made up of lobules;

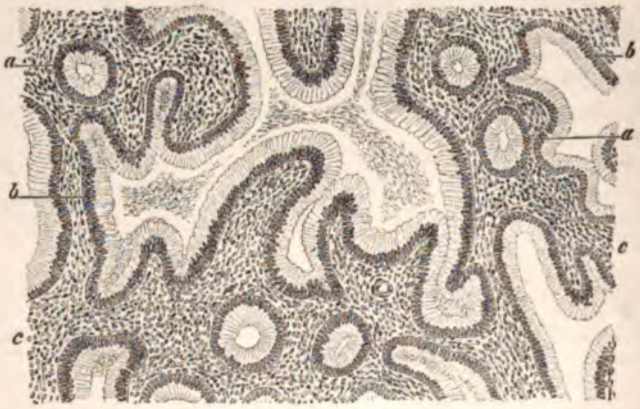


FIG. 242.—Section of a benign polyp of the large intestine, with development of new gland-tissue. *a*, Cross-section of glandular tubule; *b*, Branching glands, cut longitudinally; *c*, Stroma rich in cells. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 80 diameters.)

the texture is rather firm and tough; and here and there dilated lumina of the glands may be seen. Adenomata of the kidney, liver, and testicle present a less-developed stroma and are therefore softer. Adenomata with papillary growths are especially soft.

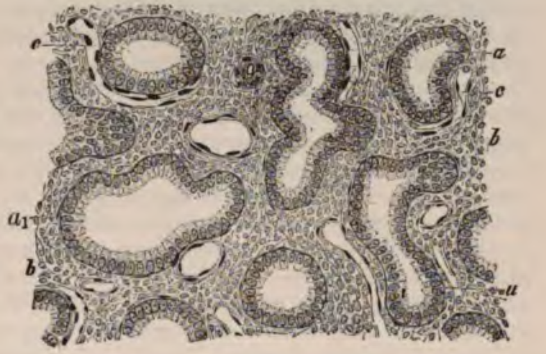


FIG. 243.—Hyperplasia of the mucous membrane of the uterus. a, a_1, Sections of glands; b, Connective tissue of the mucous membrane; c, Blood-vessels. Section through a bit of tissue obtained by curetting the uterus. (Specimen hardened in alcohol, stained with Bismarck brown, and mounted in Canada balsam. Magnified 150 diameters.)

The adenomata form a group of tumors which cannot be sharply differentiated from simple hyperplastic glandular growths, nor from other tumors of a similar character. Indeed, there appear, in the mucous membrane of the intestine and uterus, new growths which, *from the glands contained in them* (Figs. 242 and 243), *resemble adenomata, and which are reckoned by many writers, on account of the limited area of their growth, among the adenomata.* Nevertheless they ought rather to be called **glandular hypertrophies.** In the intestine they occur as the result of chronic inflammation and ulcers, but are also sometimes found in a mucous membrane which shows no traces whatever of previous inflammation or ulceration. If these growths develop in consequence of a destructive process in the mucous membrane, we must look upon them as a manifestation of *reproductive activity*, which does not lead, however, to the restoration of normal mucous membrane, but rather to the formation of tumor-like, often polypoid, masses of tissue. The glands belonging to these masses of tissue are formed, it is true, according to the pattern of normal tubular intestinal glands, with tall cylindrical epithelial cells; but they are often shaped in an abnormal fashion (Fig. 242, *b*), and in particular abnormally branched, so that we may speak of them as representing, in a certain sense, *atypical glandular new formations.* Sometimes in these tumors a certain number of glands also undergo dilatation, and *papillary excrescences* (Fig. 244, *c*) develop from the walls of these dilated portions; both of which phenomena belong to the alterations which are also observed in adenomata.

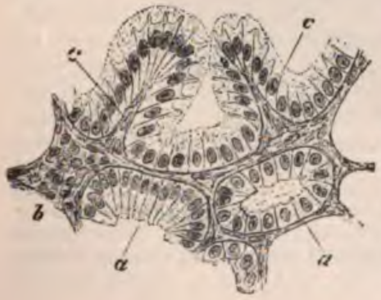


FIG. 244.—Section of a glandular polyp of the stomach, with papillary excrescences in some of the dilated glands. a, Gland-tubules with cylindrical epithelium; b, Stroma infiltrated with cells; c, Papillomatous growths inside of a gland which has undergone cystic degeneration. (Hæmatoxylin preparation. Magnified 300 diameters.)

If the signs of previous ulceration are wanting in the intestine which is the seat of glandular polyps, we must regard these growths as *hypertrophic productions,* whose cause is usually past finding out. In the uterus such glandular growths occur for the most part in later life, and usually present the characteristics of hypertrophic new formations of tissue, either following upon inflammatory processes or occurring independently of them. At the same time attention should be called to the fact that so long as menstruation continues, there occurs, at the time of the menstrual flow, a partial destruction of the mucous membrane, followed by increased growth of the epithelium and connective tissue; so that the beginning of the growth, under these circumstances, is sometimes to be considered as a reparative process. The glands developing under these circumstances (Fig. 243) are sometimes normally formed, and sometimes abnormally branched, or provided with papillary excrescences.

Tumor-like growths resembling adenomata rarely develop inside of glands; but in the course of chronic inflammations *atypical new growths of gland-tissue* often occur (cf. Fig. 187), and the only reason why they are not, as a rule, confounded with adenomata is because they evidently belong among the regular phenomena of an independent and distinct disease. But there are glandular formations in glands which are with difficulty distinguished from the adenomata. In the prostate, for example, in old age, there is an increase in size, accompanied by an actual increase in the amount of glandular tissue; and under these circumstances one

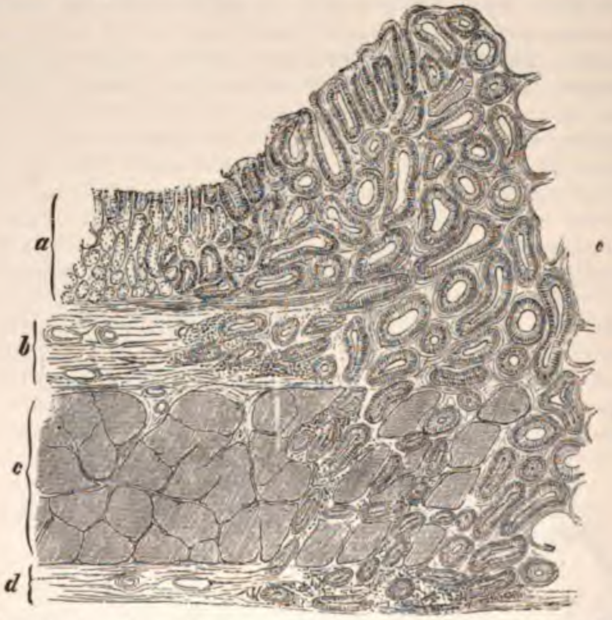


FIG. 245.—Section through the growing margin of a tubular adenoma destruens or carcinoma adenomatosum of the stomach (somewhat schematic). *a,* Mucosa; *b,* Submucosa; *c,* Muscularis; *d,* Serosa; *e,* New growth proceeding from the mucosa and infiltrating the other layers. A round-cell infiltration appears in parts in conjunction with the development of tubules. (Preparation hardened in alcohol, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 15 diameters.)

may entertain considerable doubt as to whether the condition should be termed a glandular hyperplasia or an adenoma.

The same difficulty exists in regard to the distinguishing characters of carcinomata and adenomata, and it often becomes a matter of individual judgment whether a certain tumor shall be classed as belonging to the former or to the latter of these two varieties of tumors. In the first place, we sometimes observe in the intestinal tract adenomata which, according to their structure, must be called tubular adenomata (Fig. 245), but which, at the same time, in contradistinction to the adenomata already described, present a most marked degree of malignancy and break into the surrounding tissues in the same way as a carcinoma generally does, growing from the mucosa into the submucosa, and so on into the muscularis of the intestine or the stomach, as the case may be (Fig. 245, *e*); in a word, the new growth often penetrates the entire thickness of the intestinal wall or the stomach-wall at a time when the portion of the tumor which projects into the intestine or into the stomach is still quite small. If, in judging of such a tumor, we attach the chief importance to its histological structure, we may appropriately give it the name of **adenoma destruens** or **carcinomatosum** or **malignum**; but if its behavior toward the surrounding tissues or its clinical course be chiefly considered, we shall probably prefer to call the tumor a **carcinoma adenomatosum.** It should be further mentioned that tumors which in structure begin like adenomata may later, both in the matter of structure and as regards their relation to surrounding tissues, be precisely like the cancers, and so constitute a special variety of carcinoma (cf. § 130), for which the term **adenocarcinoma** might with fitness (in view of the origin of the growth) be adopted.

Finally, it should be stated that adenomata are closely related to the group of epithelial cystomata (cf. §§ 136 and 137) and often form the first stage in the development of the latter. Consequently there are tumors which, from their origin, merit the name of **adenocystoma.**

(*c*) *Carcinoma.*

§ 130. Carcinomata develop either from a mucous membrane or from the skin or from a gland, the growth beginning in epithelial multiplication, in which the cells usually divide by mitosis. In many cases the epithelial structures first formed possess the characteristics of a gland. This is true of a great part of the carcinomata of the intestinal tract (cf. § 129), and also of the rarer cases of carcinoma of the body of the uterus. The structures first formed are glandular tubules, more or less atypical in form, and lined with simple cylindrical epithelium (Fig. 245, *e*). These tubules push their way in an outward direction from their point of origin—that is, from the mucous membrane—into the surrounding tissues. In rare cases this form of growth may be thoroughly maintained for a long time. More often, however, a more active proliferation of the epithelium takes place, resulting in the formation, at one time, of many layers of epithelium in the glandular tubules (Fig. 246, *a*, *b*), at another of solid masses and columns of cells (Fig. 247, *b*). The mode of development of the tumor is therefore very much like that of an adenoma, from which it is distinguished, however, by the increased proliferative activity of the epithelial cells and by the more markedly atypical manner in which this activity shows itself—characteristics which justify the use, as applied to this tumor, of the term **adenocarcinoma.** In the intestinal tract it is

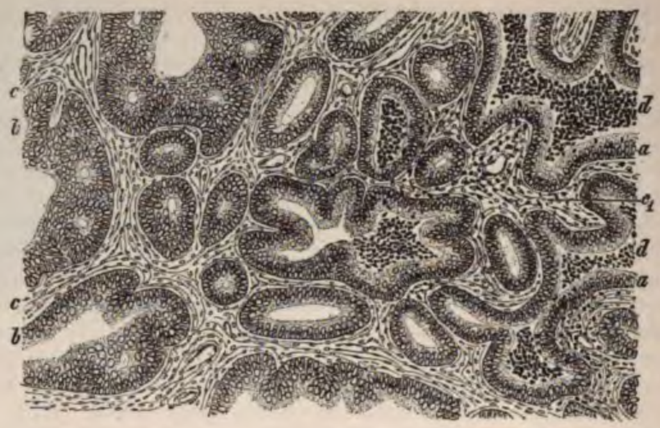


FIG. 246.—Tubular adenocarcinoma of the rectum. *a*, *b*, Epithelial gland-tubules; *c*, c_1, Stroma; *d*, Collection of leucocytes in the gland-tubules. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 80 diameters.)

the commonest variety of carcinoma, although cancers are common enough here in which from the beginning the epithelial multiplication takes place in compact cell-groups.

Cancers of the skin and of the mucous membranes which are covered

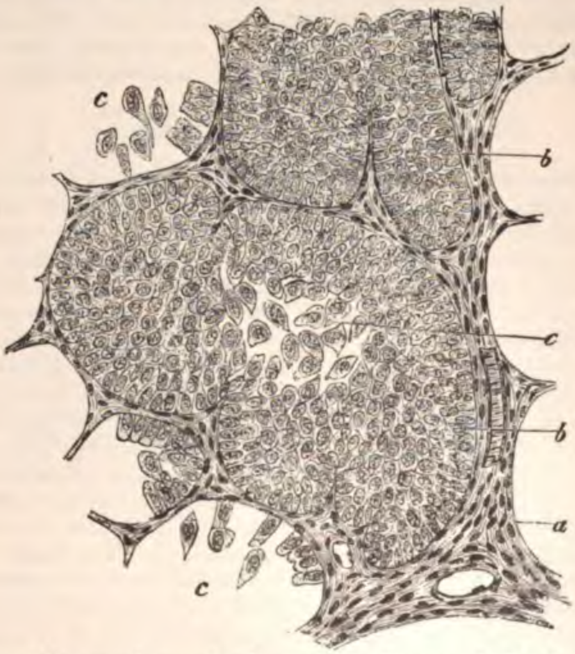


FIG. 247.—Adenocarcinoma fundi uteri. *a*, Stroma; *b*, Carcinomatous processes; *c*, Single cancer-cells. (Magnified 150 diameters.)

with stratified epithelium are usually characterized, in their development, by the formation of compact nests and columns of cells (Fig. 248, *f*, *g*), which spring from the superficial epithelium (*a*), or from the sebaceous glands or the hair-follicles, and penetrate next into the clefts or spaces of the neighboring connective tissue.

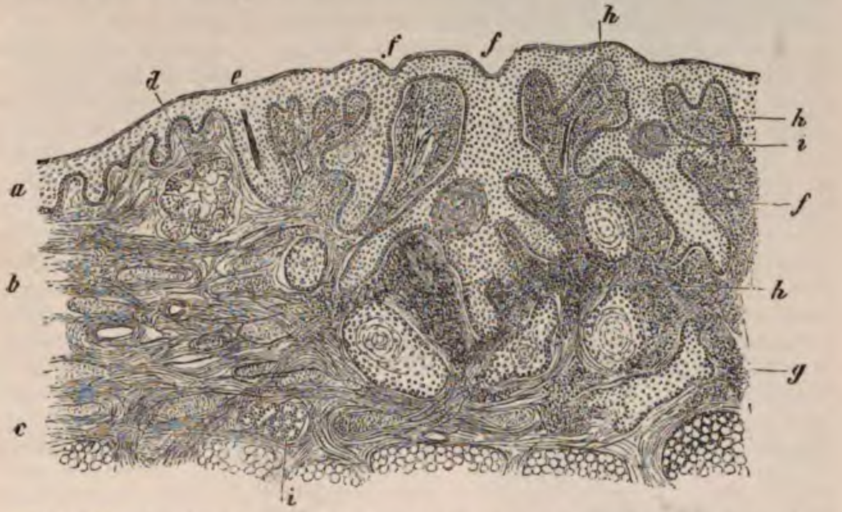


FIG. 248.—Section through a cancer of the skin in an early stage of development. *a*, Epidermis; *b*, Corium; *c*, Subcutaneous connective tissue; *d*, Sebaceous gland; *e*, Hair-follicle; *f*, Cancerous plugs connected with the epidermis; *g*, Cancerous plugs lying deeper in the tissues; *h*, Proliferating connective tissue; *i* (above and on the right side), Epithelial pearl; *i* (below), Cross-section of a sweat-gland. (Preparation stained with Bismarck brown. Magnified 20 diameters.)

In these instances, accordingly, the carcinomatous new formation appears from the outset in a pure type; that is, the proliferation of epithelial cells shows characteristics which are in general recognized as belonging to the carcinomata and as being typical of them. The skin, however, is sometimes the seat of cancers whose columns of cells possess a central lumen. Such a tumor, on section, presents the picture of elongated and often anastomosing gland-tubes. But cancers like this are rather rare.

Cancers which spring from the glands, breast, liver, kidney, pancreas, salivary glands, ovary, testicle, etc., usually display, even in the early stage of their growth, solid masses of epithelium, which, arising from parts of the glandular tissue, penetrate into the connective tissue of the vicinity. In all these organs, however, other cancers develop which more closely resemble the adenocarcinomata in their formation of structures like gland-tubules and alveoli—i.e., structures like those which have already been described when we spoke of intestinal carcinomata.

The epithelial growth proceeds usually by mitotic cell-division, and in all cell-nests of growing carcinomata—provided retrogressive changes have not set in—a greater or less number of karyokinetic figures may be found.

The connective tissue, in the beginning of the carcinomatous development, sometimes shows no appreciable change. Oftener, however, it shows indications of growth, and usually there are also infiltrations of leucocytes (Fig. 249, *k*), which may, in certain spots, lie in large masses in the tissue. Very often these leucocytes penetrate into the columns of epithelial cells. Here they cease to live, being destroyed by the epithelial cells, which doubtless utilize them for their own nourishment.

If a cancerous growth has begun to develop, it spreads with greater or less rapidity into the neighborhood. This spread of the growth is especially rapid in the case of cancers of a mucous membrane, where the breaking through into the submucosa is followed by a rapid diffusion of the cancerous new growth in the interstitial spaces of this layer. Hence, in cancers of the intestine, not only the submucosa, but the muscularis and serosa as well (Fig. 245, *e*), are soon studded with the cell-nests of the tumor, and at once begin to proliferate actively. This diffusion of the growth takes place chiefly along the course of the lymphatic channels, but a break into blood-vessels—more especially veins—is by no means a rare occurrence. In a similar manner cancer of a gland extends its development into the neighboring tissues after its growth has proceeded beyond the particular region of its origin; and it may spread far beyond the site of the first centre of growth. So, for example, in the growth of a carcinoma of the breast (Fig. 249), the connective tissue surrounding the gland becomes studded with round or spindle-shaped or cord-like

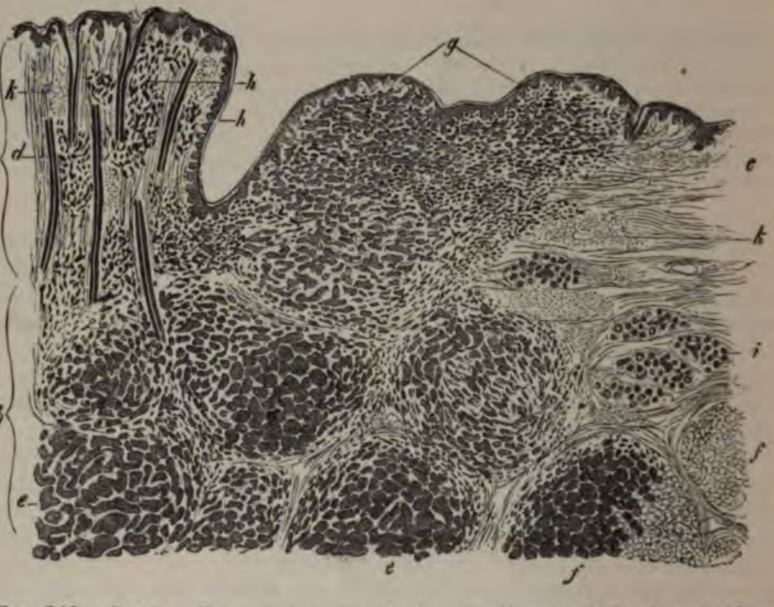


FIG. 249.—Section through a segment of a carcinoma of the breast (drawn with the aid of a basic lens). *a*, Nipple; *b*, Tissue of the mammary gland; *c*, Skin; *d*, Outlet-ducts of the gland; *e*, Carcinomatous masses occupying the position of glandular tissue; *f*, Lobules of fat already infiltrated with cancer; *g*, Portion of skin also infiltrated with cancer; *h*, Carcinomatous cell-nests in the nipple; *i*, Normal lobules of the gland; *k*, Infiltration of small cells in the connective tissue.

foci of cancer-cells (*e*, *f*, *g*, *h*); and the cancerous growth penetrates into the surrounding fat-tissue (*f*), into the skin (*g*), and often also into the papillæ of the nipple (*h*). The channels along which the cancerous growth spreads are the lymph spaces and vessels, and only a very short time is required before secondary nodules, quite separate from the original focus of the disease, make their appearance in the course of the efferent lymph-vessels.

The newly produced epithelial cells of the individual cell-nests, usually referred to in fully developed carcinoma as **cancer-cells**, show in general in their characteristics their origin from epithelium. They are relatively large and have large bladder-like nuclei. Very often, too, it is possible to recognize the character of the epithelium from which the cancer has sprung. Thus we may find, in cancer of the intestine, *cylindrical epithelial cells*, and in cancer of the skin characteristic *cells of stratified epithelium*. In many parts of the tumor, however, the characteristic cell-form is lost. When the cells develop in the interstices of the connective tissue in the form of plugs and columns, it is unavoidable that they should press upon one another, and that their shapes should undergo considerable alterations (Fig. 250). As a consequence of this the single cells, when isolated, present the greatest variety in their forms. This has led some authorities to speak of a **polymorphy of cancer-cells**; and it is literally true that the cancer-cells appear in a very great variety of shapes. But it must not be forgotten that this richness in the forms of the cells of a tumor affords no certain proof of its carcinomatous nature; in fact, irregularly shaped cells are even more likely to belong to a sarcoma.

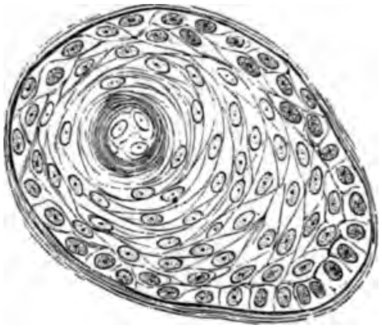


FIG. 250.—Epithelial plug from a cancer of the skin. (Magnified 250 diameters.)

In glands carcinoma forms nodular tumors sometimes sharply limited, sometimes losing themselves, without definite boundaries, in the surrounding tissues into which they send out offshoots. In mucous membranes these new growths stand out prominently in the form of fungoid or papillomatous masses, or they are spread out more flatly along the surface. At an early period of their growth they penetrate into the submucosa, and may extend even deeply into the surrounding tissues. Cancers of the skin behave in a similar manner, but their growth is usually not so rapid as that of cancers of mucous membranes. Degeneration in the new growth often causes ulcers.

§ 131. Different kinds of carcinomata have been established in accordance with their varying characteristics—such, for example, as the differences in the localities where they may begin to grow, and in the tissues from which their first development may commence; differences in the form and composition of the cells and in their mode of arrangement; differences in the manner in which the epithelial cells infiltrate the connective tissue; and, finally, differences in the amount and character of the connective-tissue stroma. Many of these distinctions, however, have to-day lost much of their significance. So, for instance, the designation of certain cancers of the skin and mucous membranes as **epithelial cancers**, or **epitheliomata**, possesses only this value—namely, that in this way the site and anatomical characteristics of a tumor may be conveniently designated, whereas formerly the term was used to indicate a distinction between epithelial and connective-tissue cancers. Other terms, such as *carcinoma medullare*, *carcinoma simplex*, *carcinoma scirrhosum*, by which it was intended to characterize the structure of different carcinomata, especially those springing from glands, also possess only a limited value; for a carcinoma does not show the same structure in all its parts or in all its phases of development.

In general the form of a cancer depends on the nature of the parent-tissue from which it springs; that is to say, in its growth the cancer repeats, with little change, a certain group of formations that are normally present in the parent-tissue. From mere *a priori* reasoning it would seem most natural to divide the carcinomata into two great groups—namely, those which start from the epithelium of a surface and those which develop from the epithelium of a gland. Theoretically one can adopt a classification like this, but in practice it is not possible to follow it in all cases without resorting to an exact histological examination. For example, a cancer of the skin springing from sebaceous glands shows in general the same characteristics as one which springs from the hair-follicles or the epidermis; and in the alimentary tract it is scarcely possible to make a division of carcinomata according to their origin from the surface epithelium or from that of the glands of Lieberkühn. Consequently, in the consideration of carcinomata in general, it is best simply to select certain chief types, which are distinguished by well-marked anatomical differences.

1. **Flat-celled epithelial cancer** commonly occurs in the skin as *skin-cancer* or *skin-cancroid* (Fig. 248), and forms a warty or a nodular tumor or a flat thickening of the skin, all of which forms are characterized by the development of large cancerous cell-nests, made up of large, polymorphous, flat epithelial cells. Degeneration of the new growth forms cancerous ulcers.

Upon scraping the cut surface of the tumor, which shows plainly its alveolar structure, a knife drawn across it scrapes up a gruel-like fluid containing plugs of cells and single epithelial cells. Within the plugs the cells are often arranged concentrically, like the layers of an onion (Fig. 250). These balls of cells may become horny and form *epithelial pearls*. Such tumors are usually called *horny cancroids*. The cancer-cells of skin-cancers are derivatives of the cells of the epidermis as well as of the sebaceous glands and the hair-follicles.

Flat-celled cancers occur also in those mucous membranes which are covered with similar epithelium—e.g., in the mouth, pharynx, œsophagus, bladder, vagina, and uterus.

2. **Cylindrical epithelial cancer** occurs, in the first place, in the mucous membranes, and most often in that of the intestine; it also occurs, but more rarely, in the mucous membrane of the gall-ducts, gall-bladder, respiratory passages, and uterus. In the last situation it arises only in those portions which are covered with cylindrical epithelium, as cancers of the vaginal portion, or of the vagina, are for the most part flat-celled. It forms soft nodular, sometimes papillary tumors, which are generally classed among the encephaloid growths.

Furthermore, this variety of cancer also develops in glands where it forms likewise nodular tumors, from whose cut surface an abundant milky fluid can be scraped.

Cylindrical-celled cancers resemble adenocarcinomata in their character (Figs. 246 and 247). From their appearance and from their mode of origin they might be called **medullary adenocarcinomata.**

3. Besides the adenocarcinomata, we also find, both in mucous membranes and in glands, medullary cancers whose feebly developed stroma contains only solid cancer-nests, without any central lumen. To such growths we apply the term **medullary carcinoma.**

4. **Carcinoma simplex** is a term given to a form of cancer which frequently grows in glands and forms rather hard nodular tumors. The cut surface appears of a bright grayish-white color, and somewhat translucent. Connective-tissue stroma and cancer-cell nests are, at least in some portions, by reason of their different colors, easily distinguishable. This is especially the case if by fatty degeneration the cell-nests have become white or yellowish white. A rather abundant milky juice can be scraped from the cut surface.

The tumor has a strong fibrous stroma (Fig. 251, *a*), which contains meshes of different shapes and sizes filled with epithelial cell-masses.

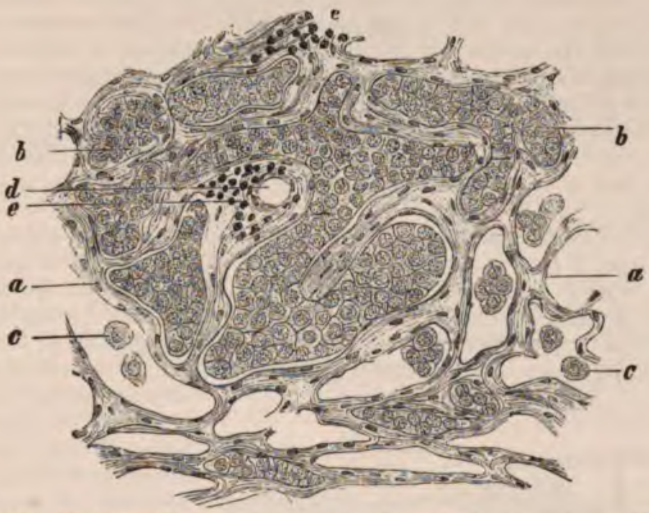


FIG. 251.—Section of a carcinoma simplex of the breast. *a*, Stroma; *b*, Plugs of cancer-cells; *c*, Single cancer-cells; *d*, Blood-vessel; *e*, Infiltration of the stroma with small cells. (Preparation stained with hæmatoxylin. Magnified 200 diameters.)

Such carcinomata are especially common in the breast, but are less often found in the pancreas and kidney.

5. A **scirrhous carcinoma,** or **scirrhus,** is one in which the cancer-cell nests are relatively small and scanty, and separated from one another by tough fibrous stroma, which gives a hard and tough consistence to these tumors.

No strict line of division can be drawn between scirrhus and carcinoma simplex. On the contrary, in a single tumor one portion often presents the appearances of carcinoma simplex, and another portion the appearances of scirrhus (cf. Fig. 249)—i.e., in one portion of the tumor the cancer-cell nests may be rather abundant and large and the stroma insignificant, while in another portion the nests are small and the stroma well developed. The hardness which is characteristic of scirrhus is best marked in those portions in which (as in Fig. 249, *g*, *h*) very small spindle-shaped cancer-cell nests are scattered throughout the connective tissue. This hardness may also owe its existence to the fact that fatty degeneration and absorption of the cancer-cells have left nothing behind but the tough connective-tissue stroma, which looks very much like scar-tissue. In this manner a soft cancer, by retrograde changes in the cancer-cells and corresponding proliferation of the connective tissue, may come to possess a scirrhous character. This happens very often in ulcerating cancers of the stomach and intestine.

Hard cancers, rich in connective tissue, occur chiefly in the breast and stomach, less often in the testicles, ovaries, and kidneys.

6. **Gelatinous carcinoma,** or *alveolar* or *colloid cancer*, occurs in the form of nodules or as a diffuse infiltration. It is found most frequently in the intestinal tract or in the breast, more rarely in the ovary, etc. Its tissue is noticeable on account of its great transparency; for the stroma, instead of inclosing the more opaque cancerous cell-nests, contains transparent colloid masses, both large and small. This transparence is often observable on the surface of the tumor—for example, in colloid cancers of mucous membranes, which develop in the form of fungoid or of papillomatous or of more diffuse growths, as the case may be. In colloid cancers of the breast the transparent nature of the tumor is only discovered after it is cut into. Often only a part of a tumor displays this character, while the rest of it appears grayish white or grayish red, like an ordinary carcinoma.

The gelatinous character of the tumor is due to a mucoid or colloid degeneration of the cancer-cell nests (Fig. 252)—a change which begins by the formation of clear drops within the cancer-cells (*d*). In the cylindrical-celled cancers goblet-cells are commonly formed. Later, these cells degenerate and are destroyed, and the drops flow together, or unite with larger aggregations of the material, already formed, to constitute a single homogeneous mass. In this way all the cancer-cells throughout large areas may be destroyed, so that of formed elements nothing remains but the stroma. In other parts nests of cells still remain within the colloid mass (*b*), and there may be still other portions which are quite free from colloid degeneration.

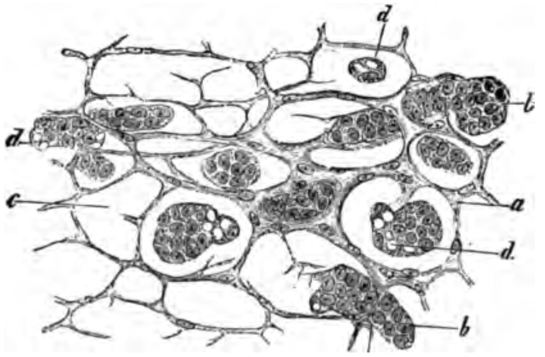


FIG. 252.—Gelatinous carcinoma of the breast. *a*, Stroma; *b*, Plugs of cancer-cells; *c*, Alveoli without cancer-cells; *d*, Cells containing colloid masses. (Preparation stained with hæmatoxylin. Magnified 200 diameters.)

7. A **myxomatous carcinoma** (carcinoma myxomatodes) is a cancer in which the stroma undergoes a change into mucous tissue (Fig. 253). Under certain circumstances a like degeneration overtakes the cancer-cells (Fig. 253, *d*), so that the tissue becomes quite translucent and gelatin-like. If the cells of the connective tissue likewise undergo destruction, the colloid areas will finally contain no cellular elements whatever. This variety of cancer occurs in the same situations where the gelatinous carcinoma is found.

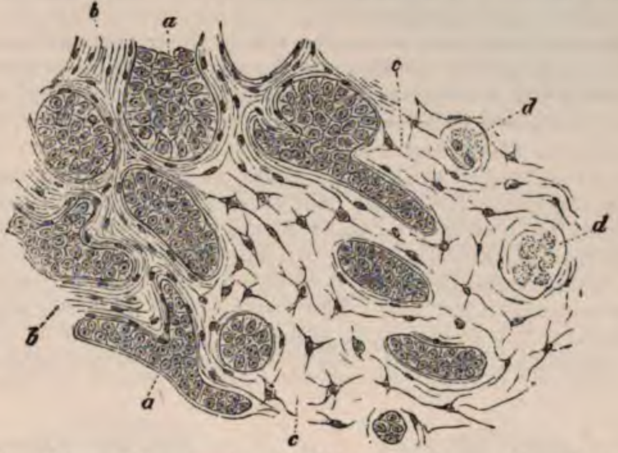


FIG. 253.—Myxomatous carcinoma of the stomach. *a*, Plugs of cancer-cells; *b*, Connective-tissue stroma; *c*, Stroma of mucous tissue; *d*, Cancer-cells which have undergone mucous degeneration. (Preparation stained with hæmatoxylin. Magnified 200 diameters.)

8. Another relatively rare form of carcinoma may develop in the following manner: the elements of the growth first undergo hyaline degeneration, and at the same time the hyaline substance and the masses of cells arrange themselves in groups in a peculiar manner. The pictures presented by sections of a carcinoma which has gone through these changes remind one of those seen in the sarcomata called cylindromata, when they have similarly undergone hyaline degeneration. Carcinomata like this have accordingly been reckoned among the cylindromata, and called **carcinomata cylindromatosa.** In a certain number of the cases the hyaline

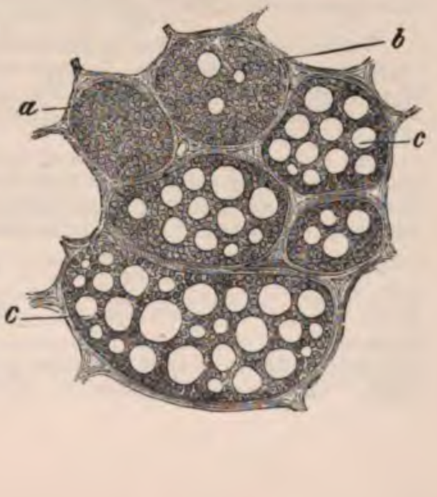


FIG. 254.—Carcinoma showing hyaline degeneration of the epithelial cells (carcinoma cylindromatosum). *a*, Cell-nest without hyaline-degenerated areas; *b*, Cell-nest with a few hyaline globules; *c*, *c*, Cell-nests in which the cells have been forced into net-like forms by the abundant formation of hyaline globules. (Magnified 150 diameters.)

degeneration involves the epithelial cells, and accordingly hyaline globules develop in the midst of the cell-nests (Fig. 254, *b*). These globules may at last become so numerous as to press the epithelial cells together in trabeculæ arranged like netting (*c*). In other cases the hyaline degeneration involves the connective tissue, and it may happen that columns of cells growing in the lymph-vessels may be separated from one another only by hyaline connective tissue.

Cancers in which there are spots which show hyaline degeneration, are observed not only in the skin and intestine, but also in glands.

9. **Giant-celled carcinoma** (carcinoma giganto-cellulare) is a name which may be applied to a form of carcinoma in which a part of the cancer-cells reach an extra large size. In some of the cases these large cells are simply hypertrophic cells which reach an extraordinary size without undergoing any other particular change in appearance, except, perhaps, that they may have several or many nuclei (giant cells). In other cases the enlargement of the cells is due to a mucoid or dropsical degeneration (Fig. 255), which causes the cells (*b*), as well as their nuclei (*c*) and nucleoli, to become very much swollen. The protoplasmic granules appear to be pushed apart by the fluid, and in the cells (*b*) and nuclei (*c*) clear drops free from granules are formed. Such cells are called physalides by some authors.

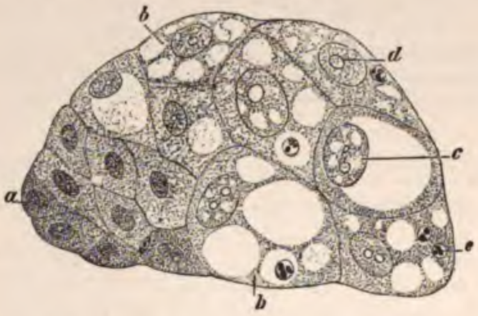


FIG. 255.—Enlarged dropsical cancer-cells from a carcinoma of the breast. *a*, Ordinary cancer-cells; *b*, Dropsical cells containing in their interior clear drops of fluid; *c*, Swollen nucleus; *d*, Swollen nucleolus; *e*, Wandering cells. (Preparation hardened in Müller's fluid, stained with Bismarck brown, and mounted in Canada balsam. Magnified 300 diameters.)

10. **Melanocarcinoma** is the last variety of cancer which requires mention. It forms gray or brown or black tumors. The pigment lies partly in the stroma, partly in the cancer-cells. Melanocarcinoma is much rarer than melanosarcoma.

We should also mention, in this place, the **pearly tumors** or **cholesteatomata** —i.e., tumors or tumor-like products which are characterized by the formation of shining-white pearly bodies. The pearls are made up of cells like scales, which are packed together in concentric layers in the form of little balls, some of which inclose cholesterin.

The most typical formations of this sort occur in the pia mater and in the brain-substance proper, where they form either solitary tumors possessing a connective-tissue capsule and resembling dermoid tumors, or multiple glistening nodules or larger round masses lying free in the pia and brain. Many authors[*]

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[*] Cf. Virchow, *Virchow's Arch.*, 8. Bd.; Eppinger, *Prager Vierteljahrsschr.*, 1875; Gross, "Contrib. à l'étude des tumeurs perlés," Paris, 1885; Eberth, *Virch. Arch.*, 49. Bd.; Chiari, "Cholesteatome des Rückenmarkes," *Prager med. Wochenschrift*, 1883; Glaeser, "Untersuch. ü. das Cholesteatom und ihre Ergebnisse für die Lehre von der Entstehung der Geschwülste," *Virch. Arch.*, 122. Bd.; Buzzi, "Cholesteatom," *Mittheil. a. d. Dermat. Klin. d. Charité*, 1888.

regard them as endotheliomata; others hold the view that they are of epithelial origin. As the scales in every respect resemble cornified epidermis-cells, and as, according to my own observation, the cell-masses may contain hairs either free or growing in hair-follicles, I am of the opinion that *the pearls are of epidermal origin*, and that accordingly these growths spring from cutaneous tissue which in fœtal life has found its way either into the pia or into the brain-substance, as the case may be. The same may be said of similar formations which are found in the pelvis of the kidney,[*] in the connective tissue of the testicle, the parotid gland, the ovary, etc., in the auditory canal, and in the cavities of the mastoid process and middle ear.[†] In all of these cases we have to do not with tumors but with epithelial collections in preëxisting spaces, the epithelial desquamation (excepting when it occurs within a tumor) being caused by inflammatory processes.

§ 132. A cancer grows first in the particular organ where it originates (Fig. 256, *a*, *b*), but often extends to the neighboring organs. The specific tissues—such as parenchymatous gland-cells, muscle-fibres, and bones—atrophy under the pressure of the growing tumor, while the connective tissues take on active proliferation under its influence.

If epithelial germs from a carcinomatous focus find their way into a lymph- or blood-vessel, a **metastasis** forms at the point where these germs lodge and develop. This occurs very often in the affected organ itself (Fig. 256, *b*). In other cases these germs appear very early in the lymph-vessels outside of the organ primarily affected (cf. Fig. 192), or in the nearest lymph-glands. Often, too, the proliferating epithelial cells manage to get into the blood-current, and are swept away by it. Thus,

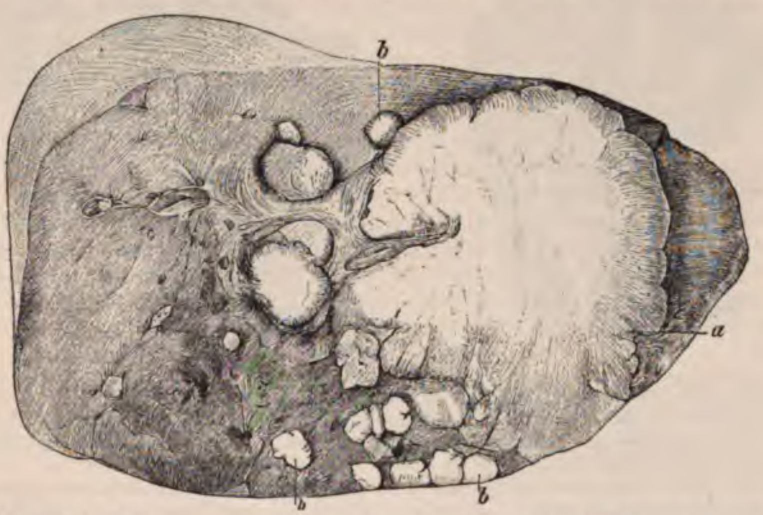

FIG. 256.—Primary carcinoma of the liver (*a*), with multiple metastases (*b*) within the liver itself. (Reduced more than one half in size.)

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[*] Rokitansky, "Lehrb. d. pathol. Anat.," iii., 1855; and Beselin, *Virch. Arch.*, 99. Bd.

[†] Kipp, *Arch. f. Augen- u. Ohrenheilk.*, iv.; Lucae, *Arch. f. Ohrenheilk.*, i., 1873; Steinbrügge, *Zeitschrift f. Ohrenheilk.*, viii.; Wendt, *Arch. d. Heilk.*, xiv., 1873; von Tröltsch, "Lehrb. d. Ohrenheilk."

for example, in cancers of the intestinal tract very often epithelial cells break into some branch of the portal vein and are carried to the liver, where they develop into metastatic nodules.

By multiplication of the transplanted cells a cell-nest is formed (Fig. 257), which swells out the vessel into which the cells have floated, while the liver-cells are compressed and undergo atrophy. Then with the assistance of the vascular and connective-tissue system of the liver, which develops a connective-tissue stroma and new blood-vessels, a secondary nodule is formed which resembles in all points of its structure the parent-growth from which it originated. The columns of liver-cells in its vicinity are either displaced and compressed, or the cords of cells belonging to the secondary growth push their way directly through the liver-cells. The latter happens in this way: the growth of the cancer-nodule takes place mostly on the periphery in the open capillary vessels (Fig. 258), so that the blood-capillaries are filled one after another with cancer-cells. As the latter develop the liver-cells atrophy and disappear.

Fig. 257.

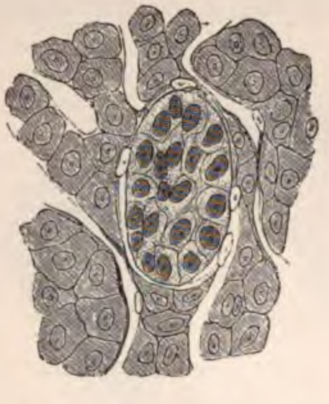

Fig. 258.

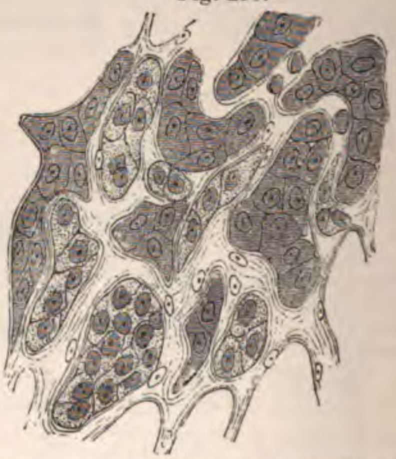

FIG. 257.—Section through an aggregation of very young cancer-cells, lodged like an embolus within a capillary of the liver. The parent-growth was an adenocarcinoma of the stomach. (Preparation stained with hæmatoxylin. Magnified 300 diameters.)

FIG. 258.—Metastatic cancerous development in the liver-capillaries, following upon carcinoma of the pancreas. Within the capillaries, both cancer-cell nests and connective tissue have developed. (Preparation stained with alum carmine and mounted in Canada balsam. Magnified 250 diameters.)

The epithelial elements of the metastatic cancer-nodules are to be regarded as purely derivatives of the cells transplanted from the primary nodule. The tissue in which the secondary nodule is located furnishes only the vascular and connective-tissue portions of the new growth.

§ 133. **Retrograde changes** occur extensively in carcinomata, and often terminate in the destruction of a part of the new growth. Not a few of the cells found in the juice scraped from the cut surface of a cancer are almost always *fatty-degenerated* or *necrotic*, and this is especially true of soft, rapidly growing tumors. If the fatty degeneration is considerable the portions affected have a white opaque appearance, and may disintegrate into a gruel-like mass which either thickens into a caseous material or becomes absorbed. If only the cancer-cells are affected by the fatty degeneration, as is usually the case, the alveolar contents are then especially prominent, by reason of the contrast between their dull-white color and the more gray or grayish-red or shining-white stroma.

In tumors which are located superficially in an organ, or stand up above the level of the surface of the body, the absorption of the disintegrated cancer-cells causes a central depression, a hollow—the **umbilication of cancer.** In cancers which have a firm stroma, and in which a hyperplasia of the connective tissue keeps pace with the wasting away of the cancer-cells, the original cancer-nodule may in this way change into a firm mass of connective tissue which contains few or no cancer-cell nests. This occurs with special frequency in scirrhus of the breast and of the stomach.

Mucous degeneration and *dropsical degeneration* have already been referred to in § 131. Partial *amyloid degeneration* of the stroma has been seen a number of times. *Calcification* is most often seen in skin-cancer, but is quite rare anyway.

Necrotic changes in carcinoma, and the **ulcers** resulting from them, are of great importance, since in this way even large new growths may be destroyed. Cancer-nodules in the intestine, for instance, are destroyed in this manner, so that in a short time after the nodule has formed, its place may be taken by an ulcer which presents scarcely a trace of the preceding tumor. If the ulceration has not progressed too far, a little of the old tumor may remain in the form of nodules and papillary growths at the bottom and along the margins of the ulcer; but if the ulceration has advanced still further, the bottom of the ulcer presents a smooth and clean appearance, and seems to consist only of hard connective tissue, while the edges form an elevated wall about it, at times studded with papillomatous or nodular growths. Sometimes, finally, the margins are also destroyed, and the ulcer then appears like a non-carcinomatous one with indurated base. Even a section may at times leave us in doubt as to whether cancer-cell nests still exist in the tissue or not.

Carcinomata of the skin or of the breast or of other subcutaneous glandular organs may undergo superficial necrosis and form ulcers just as do the cancers of mucous membranes.

In the floor of the ulceration there is always to be found a greater or less degree of inflammatory infiltration, and a new formation of connective tissue results, which sometimes reaches very considerable proportions. Sometimes quite extensive growths of granulation tissue develop in the ulcer, and rise like fungous growths above the level of the surrounding surface. They are distinguished from other granulations chiefly by the cancerous cell-nests which they contain.

§ 134. The **etiology of cancer** has not been satisfactorily cleared up by such investigations as have been made up to the present time.

According to the result of histological investigation, the growth of a cancer is due to the pathological penetration of epithelium into connective tissue. The cause of this process may be looked for in a diminution of resistance offered by the connective tissue, or in an increase in the proliferating power of the epithelium, or in a simultaneous exhibition of both. The last corresponds best to the conditions actually observed. The idea of a diminished resistance of the connective tissue to the advancing epithelial cells is supported not only by the histological appearances of sections made through cancerous nodules in the early stages of development, but also by the fact that cancers occur most often in advanced age and at a time when it can be demonstrated that atrophy of the tissues has set in. In support of an increase in the power of multiplication of the epithelial cells may be mentioned their luxuriant growth, which exceeds even that observed in regenerative processes; in fact, in a given area more nuclear mitotic figures may be found in growing cancers than in simple regenerative new growths. At the same time there occurs what may be termed a metaplasia of the epithelium, in that the newly formed cells possess morphological and physiological characters other than those of the epithelium from which the new growth springs.

The cause of the increased proliferative activity on the part of the epithelium, and of its change into cells which remind one more of embryonic epithelium, is not known. In part of the cases (cf. § 109, Fig. 190) the cancerous development follows immediately upon chronic irritations (action of concretions upon mucous membranes, or of dirt upon the skin), or upon ulceration and the formation of cicatrices (ulcers in the stomach and intestine, lupus cicatrices in the skin), or upon the development of granulation growths (lupus carcinomata), in all of which processes the epithelial cells are in part subjected to altered conditions of nutrition, and in part are displaced, so that often they are lodged among the deeper layers of the tissues. There can be very little doubt that these changes, together with the altered character of the connective tissue, give rise to the development of a cancer. Nevertheless it is impossible to say why precisely similar conditions at one time produce a carcinoma and at another do not.

In modern times, and especially quite recently, *the idea has been advanced*, by a number of authors, *that cancer may be a parasitic affection*. Some have looked for the cause in Schizomycetes, others in Protozoa. In support of this hypothesis it may be said that there are doubtless both Schizomycetes and Protozoa which, when they become colonized in the body, cause proliferation of the tissues. Quite lately the further statement has been made that in cancer-cell nests there are often found lying inside the cells structures of various shapes which resemble Protozoa, and especially coccidia. *But the finding of all these organisms does not warrant the conclusion that true cancer is really a parasitic affection.* So far as the presence of parasites has been definitely demonstrated, it has always been in growths which cannot be called genuine cancers; and, furthermore, the spherical, oval, spindle-shaped, and sickle-shaped hyaline and granular bodies which have been described as occurring in cancer may be otherwise interpreted. They are partly products of retrograde metamorphosis, such as cornification, colloid degeneration, and fatty degeneration of the epithelium; partly products resulting from the reception of leucocytes into the epithelial cells, followed by a degeneration and disintegration of the leucocytes; partly products of a nuclear division which is pathological, atypical, or in one way or another distorted; and partly products of an altered cell-division or of the inclusion of one cancer-cell in another.

(*d*) *Epithelial Cystomata.—Cystadenoma and Cystocarcinoma.*

§ 135. The tumors which may be grouped together under the name **epithelial cystomata** have this in common: they all contain cysts which are visible to the naked eye. It is advisable to separate the cystomata from the simple cysts, which result from the retention of secretion in preëxisting tubes or cavities lined with epithelium. The distinguishing characteristic, and the one which determines the diagnosis, is the fact that *in cystoma there is an actual new formation of tissue;* and, further, it is a fact to which attention should be called that the differences which are observed in this new formation of tissue afford sufficient grounds for dividing cystomata into different forms.

The number of cavities in a cystoma varies greatly, and from this starting-point we may make a division into *one-chambered* or *unilocular cystomata*, and *many-chambered* or *multilocular cystomata*. Sometimes the number of chambers is so great that it would be well-nigh impossible to count them (cf. Figs. 259 to 271).

Epithelial cystomata occur most frequently in the ovaries, mammæ, testicles, liver, and kidneys—rarely in the skin.

Multilocular cystomata of the ovary very often form extensive tumors, which weigh from ten to twenty kilogrammes or more, and which are composed of cysts of different sizes (Fig. 259). Usually the

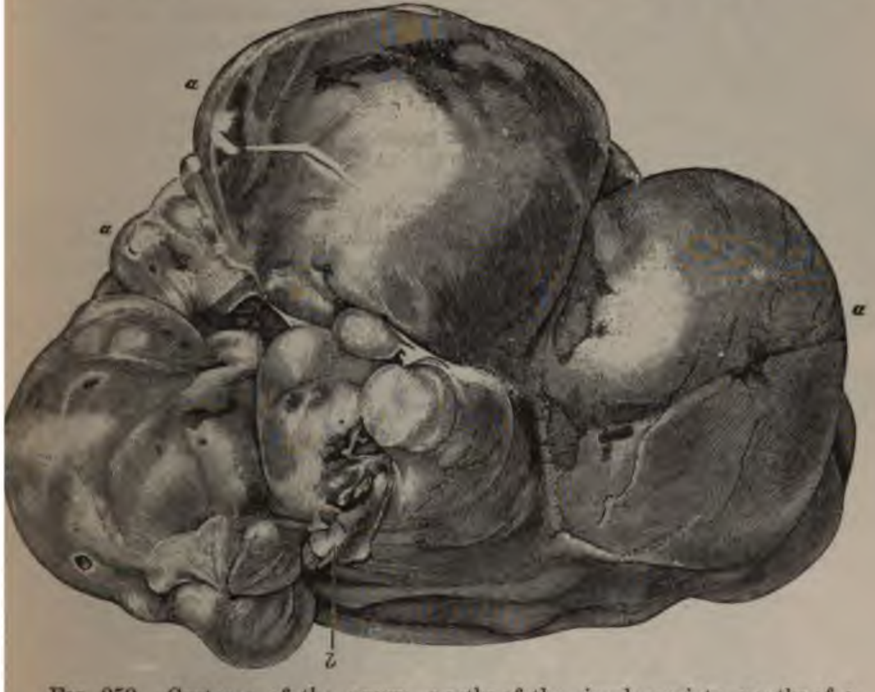

FIG. 259.—Cystoma of the ovary—partly of the simple variety, partly of a papillary character. *a*, Smooth-walled cysts; *b*, Papillary growth which has broken through a cyst-wall. (It is soft and covered with the ordinary cylindrical epithelium of mucous membranes.) There were metastatic nodules in the peritoneum. (Reduced by about one third.)

arrangement of the parts is such that numerous little cysts lie close beside a few larger ones (Fig. 259); the little ones sometimes projecting outward from the walls of the larger cysts, sometimes forming more complicated combinations among themselves. In rare cases the whole tumor is made up of small cysts, so that the section presents a honeycombed appearance (Fig. 260). Usually the tumors possess portions where the tissue resembles fine sponge, and other portions where it is more like marrow, both of these portions being located here and there between the cystic masses; but the amount of such tissue may be slight.

The walls of the cysts now under consideration are smooth and glistening, sometimes more like a smooth, stretched mucous membrane, sometimes more like a serous membrane. The cysts contain a fluid which is either clear or clouded by white flakes and granules, or colored red or brown by blood or blood-pigment. Sometimes this fluid is tenacious and plainly mucoid in character; at other times it is more serous, like the fluid of a transudation. According to Pfannenstiel, the mucoid character of the cyst-contents is due to the presence of pseudomucin (cf. § 65).

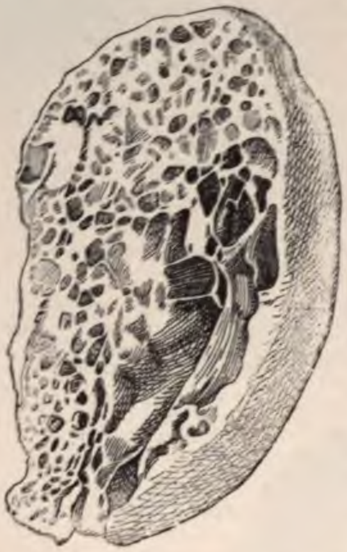

FIG. 260.—Section of a part of a multilocular cystoma of the ovary. (Reduced about one sixth.)

A second variety of ovarian cystoma which also is of rather common occurrence, and which may greatly resemble in external appearance the form already described, is to be distinguished from it by the presence, in

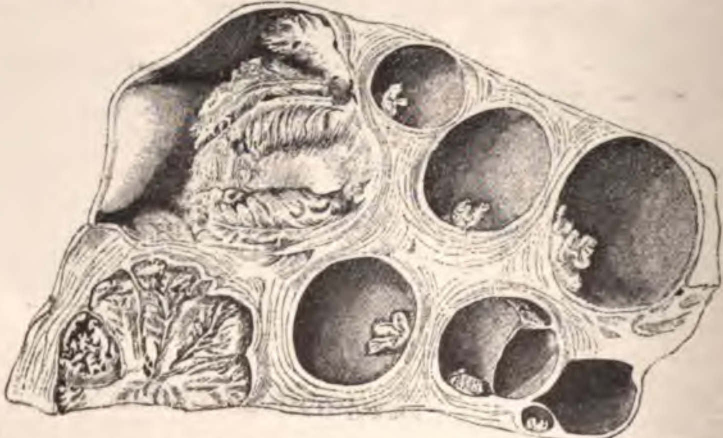

FIG. 261.—Portion of a papillary cystoma of the ovary, seen in section. (Drawn from a specimen hardened in chromic acid. Four-fifths life size.)

some or all of its cysts, of *papillary growths* (Fig. 261), which sometimes are very small and sometimes are enormously developed, and which, under certain circumstances, may fill up most of the lumen of the cyst, or may even break through and appear upon the outer surface of the tumor (Fig. 259, *b*).

In order to separate the two forms, the name **simple cystoma** may be given to the first, and **papillary cystoma** to the second. Many authors call the latter *cystoma proliferum.*

The **cystomata** which occur **in the testicle** are usually of the smooth-walled multilocular variety (Fig. 262), whose cysts reach only a moderate size.

Cystomata in the liver occur usually in the form of single cysts or of small groups of cysts scattered here and there throughout the liver-substance (Fig. 263, *d*); but the cysts which develop may also attain a considerable size (*c*); it is also possible for the liver-tissue to be replaced throughout large areas by a tissue made up wholly of cysts (Fig. 263, *e*, *c*).

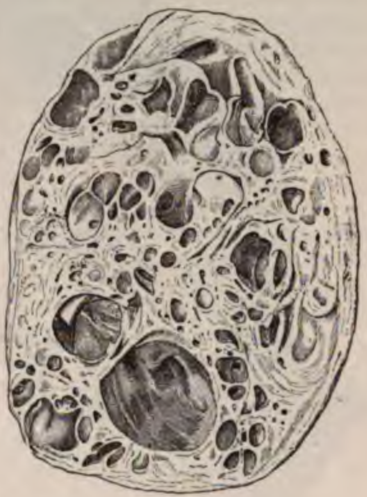

FIG. 262.—Section through an adenocystoma of the testicle of a four-year-old boy. (Life size.)

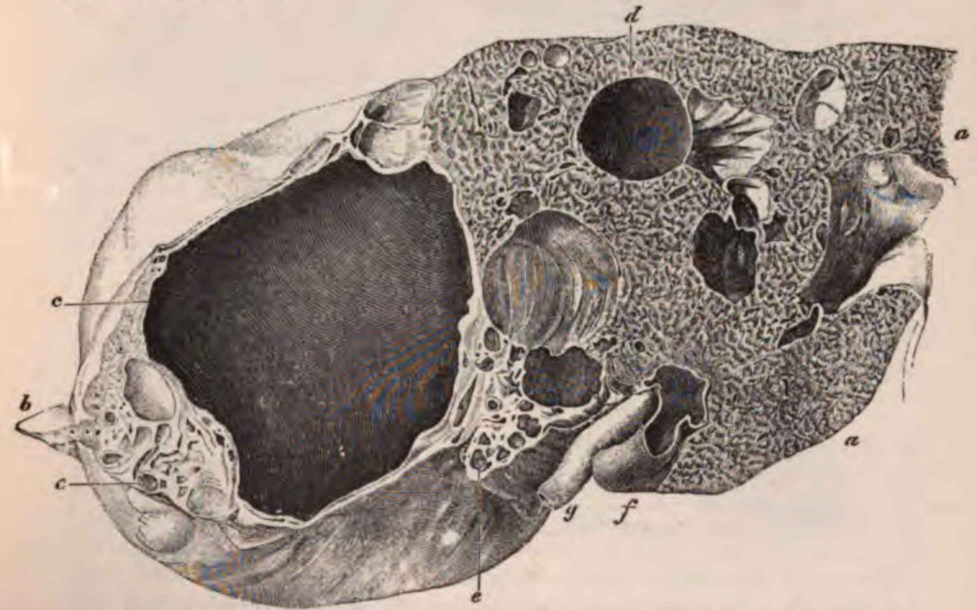

FIG. 263.—Multilocular cystoma of the liver, seen in section. *a*, Parenchyma of the liver; *b*, Membranous margin of the left lobe; *c*, *d*, Two of the larger cysts; *e*, Group of smaller cysts, separated from one another only by connective tissue; *f*, Portal vein; *g*, Hepatic artery. (Two-thirds life size.)

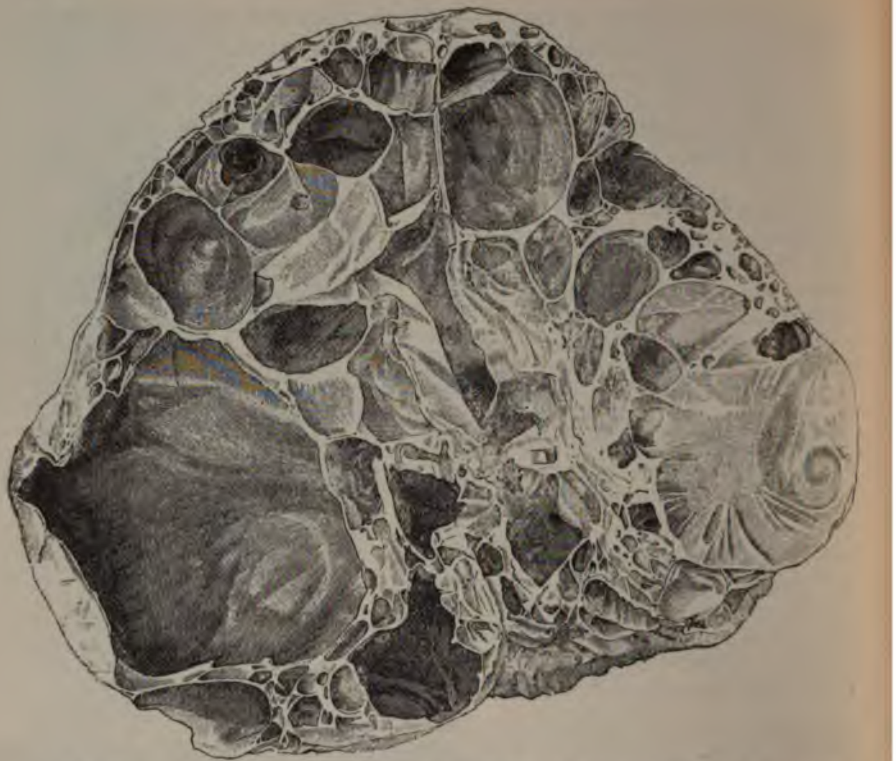

FIG. 264.—Cystoma of the kidney, in section. (Eleven-fourteenths life size.)

Cystomata of the kidney are usually large tumors made up of cysts which vary from a pea to a walnut or even a hen's egg in size (Fig. 264), and between which at most only a trace of kidney-tissue can be demonstrated. However, cases are also seen in which the cysts are all small, so that the surface of a section of the kidney presents a porous appearance

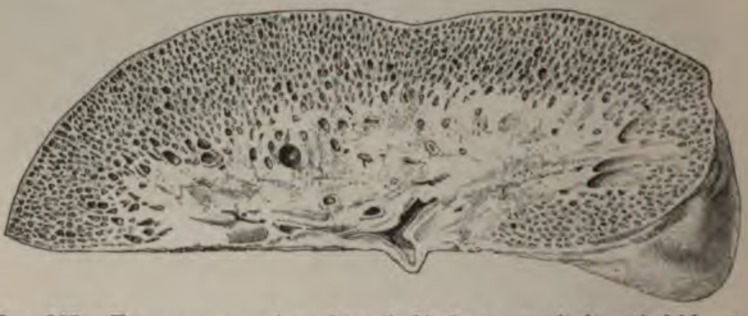

FIG. 265.—Transverse section of one-half of a congenital cystic kidney, with small cysts (from a new-born child). The kidney measured 12.5 cm. in length, 9 cm. in breadth, and 5 cm. in thickness. The cortex presented throughout a spongy appearance, with small cavities. In the medullary portion, on the other hand, there were very few cysts. (Life size.)

(Fig. 265); and yet one can still recognize, in such a section, the general anatomical features of the organ.

The **cystic tumors** which appear **in the breast** have a general resemblance to those which occur in the ovaries, but they differ in two respects: the cysts belonging to the former are usually smaller, and the intervening tissues are more strongly developed. Moreover, that form of cystic tumor which is associated with the formation of papillary excrescences occurs far more frequently in this locality, and the accompanying proliferation of the connective tissue of the breast often lends a peculiar aspect to the new growth, in consequence of which many of these cystic tumors of the breast are apt to be classified, according to the character of the tissue, as *cystosarcomata*, *cystofibromata*, and *cystomyxomata*. However, there are also cases in which the breast is the seat of a **papillary cystoma** (Fig. 265), whose structure follows exactly that of the ovarian cystomata; and consequently these tumors must be separated from the connective-tissue group and reckoned among the epithelial tumors.

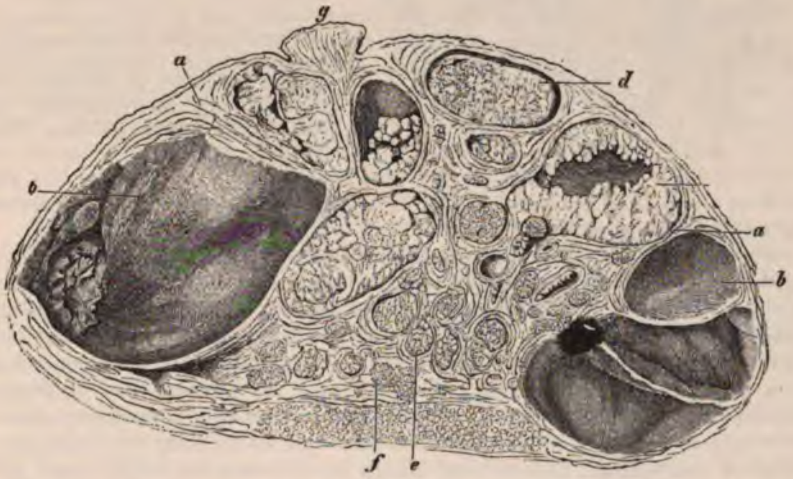

FIG. 266.—Papillary cystoma of the breast. *a*, Stroma; *b*, Smooth-walled cysts; *c*, Cysts studded on the inside with papillary growths; *d*, Cysts completely filled with papillary growths; *e*, Small encysted papillary growths; *f*, Adenomatous growths; *g*, Nipple of the breast. (Reduced in size by about one third.)

In rare cases papillary cystomata appear in the **skin** in the form of well-defined nodules, which vary in size from that of a walnut to that of an apple. The interior of the cysts is closely filled with papillary excrescences, and these may also at times break through so as to appear on the outside of the cyst. These tumors probably develop from *atheromata* of the skin or of the subcutaneous tissue—i.e., from sebaceous cysts, which are formed by the dilatation of epithelial canals in the skin, such as the ducts of hair-follicles or sebaceous glands, or pathological inversions of the epithelium (*Epitheleinstülpungen*) in the corium or subcutaneous tissue. Furthermore, papillary cystadenomata may also have their origin in the remains of branchial fissures.

§ 136. The **development of a cystoma** proceeds from the preëxisting glandular tissue, so far, at least, as one may judge from the anatomical investigation of suitable specimens. Cystomata which develop out of a depot of retained secretion, and in which the proliferative process establishes itself only at a later date, are of the single-chambered variety, whether the cyst-cavity be smooth-walled or studded with papillæ; for, under certain circumstances, the development of papillæ takes place only after the cyst has existed for a long time.

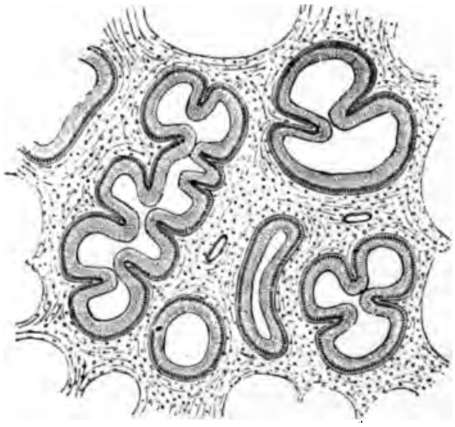

Fig. 267.—Section of a papillary cystadenoma of the ovary. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 40 diameters.)

The **multilocular** smooth-walled and papillary cystomata generally spring from pathological glandular new growths (Fig. 267)—i.e., from **adenomata,**—and they may therefore be appropriately termed **adenocystomata.** The alteration of the ducts of the glands into cysts is a result of retention, and the secretion so retained varies according to the nature of the cystoma.

The development of *adenocystomata of the ovary* takes place either in malformed or in normal ovaries, and is characterized by the formation of tubular glands (Fig. 267) which closely resemble the embryonic tubular glands of the ovary. It is not impossible that remains of these fœtal glands form the starting-point for the new growth, but this has not yet been proved. In favor of the existence of a local congenital predisposition to such a growth may be mentioned the fact that ovarian cystomata often appear on both sides. The smooth cysts are lined with simple cylindrical epithelium, the cells of which are of varying height and often present appearances of mucous degeneration.

Cystoma-formation in the kidneys, so far as it affects the whole kidney, is usually referable to some *disturbance* in development, and accordingly most of the cases observed are in the new-born or in very young children. The predecessors of the cysts are, in the first place, atypically formed tubules (Nauwerck, Hufschmid, von Kahlden), in which papillary excrescences may often be observed. Furthermore, a more or less decided proliferation of connective tissue can be made out in the vicinity of these tubules (von Kahlden). Besides the tubules, Mueller's capsules may also, through the influence of retained secretion, undergo dilatation into cysts; and under these circumstances we may take it for granted that urine constitutes the chief, if not the sole, contents of the cysts. As cystomata of the kidney may also develop in later life, it is probable that atypical tubules may develop in kidneys which are not in any manner malformed, and they may later, through the medium of retained secretion, become transformed into cysts.

Pathological proliferation of the walls of the gall-ducts furnishes a basis for the development of cysts in the *liver;* and, as a result of this proliferation, at different points numerous gland-tubules appear in the periportal connective tissue. The fully developed cysts are lined with a simple epithelium. The histological examination furnishes no grounds for the belief that these tumors originate in some congenital malformation. The nearest suggestion of such an origin lies in the coincident appearance of cystomata of the liver and kidney.

Cystomata of the testicle usually develop from gland-tubules which are lined with cylindrical (less often squamous) epithelium, and whose structure is materially different from that of the normal tubules of the testicle. It is probable that the adenomatous growth usually occurs in pathologically developed testicles; and as pointing to this conclusion, the following facts may be mentioned: first, that these growths occur at an early age; second, that other pathological tissues—as, for example, cartilage—are found quite frequently in the adenomata and adenocystomata of the testicle (cf. § 137); and third, that the character of the epithelium varies (Fig. 272).

The *development of a multilocular cystoma* begins in the breast with an *atypical growth of new gland-tissue*, which presents the characteristics of tubular glands. The epithelial lining of the tubules is composed of a simple cylindrical epithelium, whose height varies in different cases. The connective tissue may be only very slightly developed, so that the neoplasm presents the appearance of a pure *adenoma;* but it is just here in the breast that the growth of glandular tissue is often accompanied by a marked growth of fibrous tissue, which gives to the tumor the characteristics of an *adenofibroma* (cf. Fig. 196).

The **development of papillary excrescences**, which may occur either in simple or in multilocular cystomata, and which have been classified by some authorities as a special group of *papillary cystomata*, begins either immediately upon the formation of new glands, or else takes place only after the cysts have become fully developed. In the latter event simple retention cysts may form the basis from which the papillary growths spring.

If papillary excrescences develop in an adenoma whose glands present no cystic dilatations, an adenoma papilliferum will be formed (cf. Fig. 241). The development of cysts leads to the formation of a *cystoma papilliferum*.

The papillæ which are found in **ovarian cysts** are usually slender single-stalked or branched structures (Fig. 268, *a*), and are made up of a connective tissue very rich in nuclei. In some cases the papillæ are very thick and plump. They are usually covered with a tall cylindrical epithelium (Fig. 268, *c*), whose cells have the form of mucus-generating goblet-cells, and produce a secretion which can be drawn out like tough mucus, and which contains many cast-off epithelial cells (*d*) that have undergone mucous degeneration. Other cystomata have cubical epithelium, and still others ciliated epithelium. Finally, in some papillary ovarian cystadenomata the epithelial lining of the cysts consists of *stratified cylindrical epithelium* (Fig. 269). In these cases, which are not altogether rare, the new growth of epithelium decidedly preponderates. Frequently, as a result of this, the cysts become filled with a marrow-like growth, which gives to the neoplasm, even under naked-eye inspection, a peculiar medullary or encephaloid appearance.

As long as ovarian cystomata have a simple epithelial lining they are benign tumors; but when they begin to develop papillæ somewhat vigorously they may already be looked upon as possessing a certain degree of local malignancy, inasmuch as at this stage the papillæ may break through on the surface (Fig. 259, *b*), and may even, under certain circumstances,

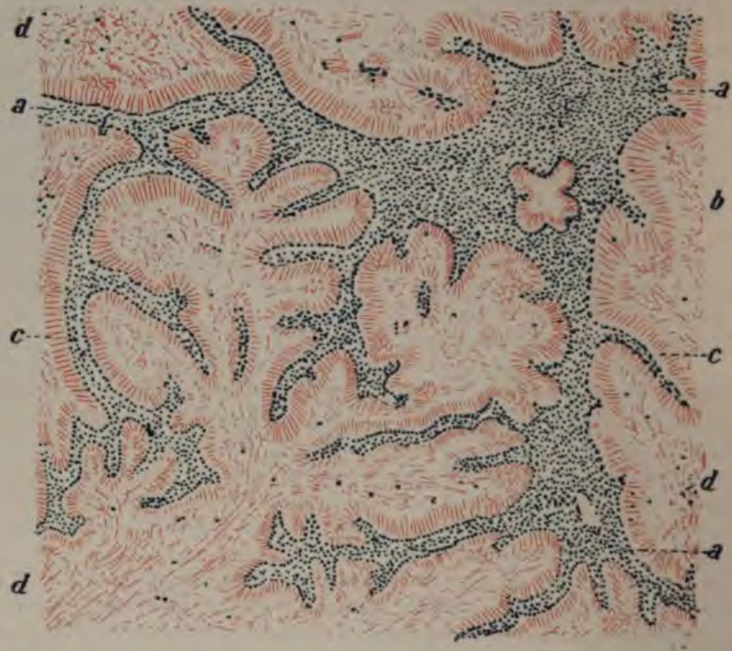

Fig. 268.—Papillary cystoma of the ovary. *a*, Stroma with papillæ; *b*, Gland-tube with small papillæ; *c*, Tall cylindrical epithelium which lines the cyst-cavities and covers the papillæ; *d*, Mucus filled with cells, in the interior of the cysts. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 150 diameters.)

spread over the peritoneum. *When the development of epithelium becomes more pronounced, the malignancy in turn increases*, and this change is shown in two ways: the growth invades to a greater and greater degree the broad ligaments, permeating the tissues like an infiltration, and causing cauliflower growths to appear upon them; and, in the second place, it gives rise to metastases in the peritoneum or elsewhere. According to its behavior the tumor must be classed as a **malignant papillary cystadenoma** or as a **papillary cystocarcinoma.** It is a remarkable circumstance that the metastases sometimes show in their structure the characteristics of an ordinary carcinoma.

Papillary cystomata may manifest in the **breast** the same behavior which they do in the ovary; but in the former region the cystomata with slender branching papillæ are on the whole rare. The epithelial lining in these forms of tumor is usually strongly developed, and consists of several layers of a stratified epithelium, which gives a medullary appearance to the contents of the cysts (Fig. 266, *c*, *d*, *e*). This abundant growth of the epithelium indicates in this case, also, the degree of malignancy of

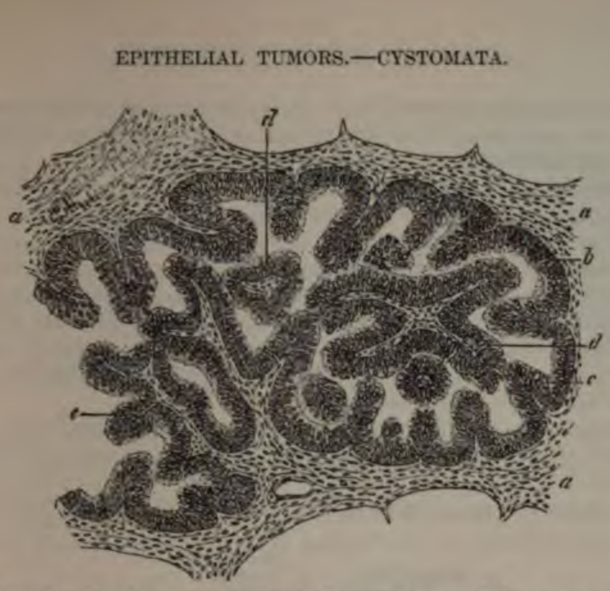

FIG. 269.—Section from a papillary adenocystoma of the ovary. *a*, Stroma; *b*, Epithelium; *c*, *d*, Papillæ. (Preparation hardened in Müller's fluid and alcohol, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 80 diameters.)

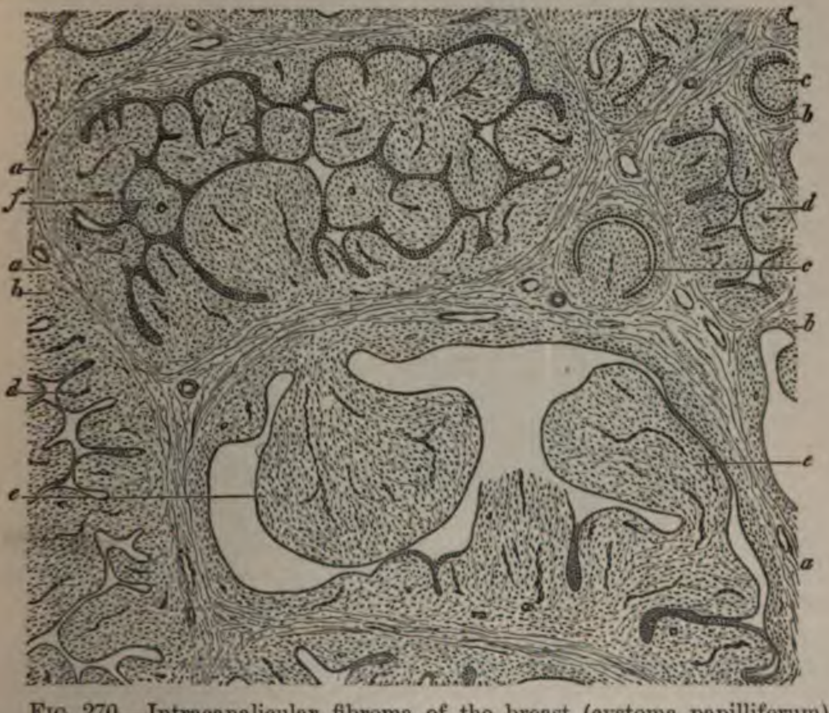

FIG. 270.—Intracanalicular fibroma of the breast (cystoma papilliferum). *a*, Dense fibrous tissue lying between the canals; *b*, Pericanalicular tissue, rich in cells; *c*, *d*, *e*, Nodular intracanalicular growths, cut longitudinally; *f*, Intracanalicular growths, cut transversely. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 25 diameters.)

the tumor,—a malignancy which finds its expression in the formation of cancerous metastases, so that the tumor merits the name of **malignant papillary cystadenoma** or **papillary cystocarcinoma.**

If, in an adenoma of the breast, the pericanalicular connective tissue develops with especial activity (see the pericanalicular fibroma represented in Fig. 196), it often happens that this connective tissue forces its way somewhat abruptly into the lumen of the gland-tubules in the form of thick prominences (Fig. 270, *c*, *d*, *e*), and in this way forms a peculiar kind of *papillary cystoma*, in which the mass of the papillæ which grow into the glands and into the cystic dilatations of the glands is so great that it seems just to describe the tumor as an **intracanalicular papillary fibroma** or as a *papillary cystofibroma.*

The intracanalicular papillary fibromata appear usually in the form of small nodular tumors whose individual nodes are made up of a group of glands modified, in the manner described above, by a new growth of connective tissue. The growth has usually definite limits, but in certain cases it takes on a more vigorous development, and in that event wide cystic cavities are developed which become filled with nodular and polypoid or compressed leaf-like fibrous excrescences (Fig. 271). Such cysts are for the most part quite numerous, but there are cases in which the entire growth is composed of only a few cysts, or even of only one cyst. If polypoid and papillomatous excrescences in a cyst press hard against

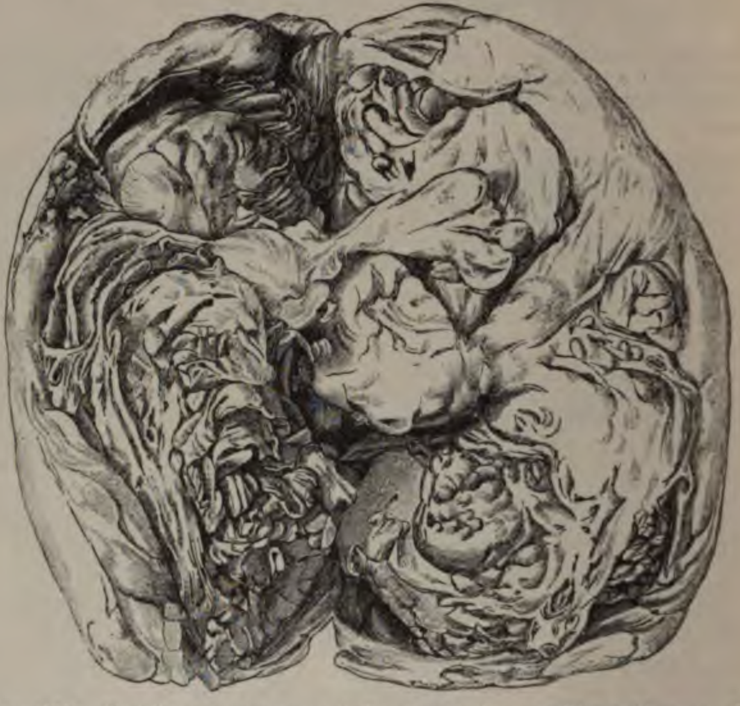

FIG. 271.—Papillary cystoma or intracanalicular papillary fibroma of the breast, laid open by a longitudinal incision. (One-half life size.)

the cyst-wall they may break through it, and may even perforate the overlying skin and appear on the outer surface of the body.

The polypoid growths of the cystomata just described often show an abundance of cells in the new growth of connective tissue, or they may present portions where the tissue appears to be myxomatous in character; and on this account the tumors have been classified among the sarcomata or among the myxomata, as the case may be, and the names *papillary cystosarcoma* and *cystomyxoma* have been given to them.

The leaf-like structure which these tumors exhibit on section, by reason of the compression of the polypoid excrescences which grow within the cysts, has led to the application of the term *sarcoma phyllodes*.

3. *Teratomata and their Relations to Monogerminal and Bigerminal Implantations and to Remains of Fœtal Structures.*

§ 137. The term **teratoma** or **teratoid tumor** is applied to a peculiar sort of new growth, which usually presents a complicated structure, and

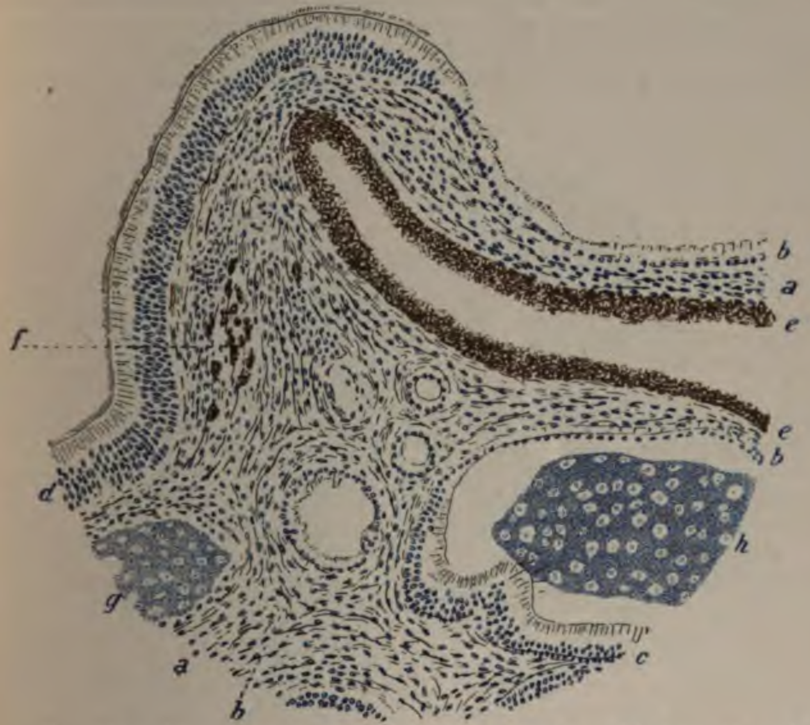

FIG. 272.—Congenital adenocystoma of the testicle, with formation of pigment and cartilage. (Section from Fig. 262.) *a*, Connective-tissue stroma; *b*, Simple cubical epithelium; *c*, Stratified cylindrical epithelium; *d*, Stratified ciliated cylindrical epithelium; *e*, Pigmented epithelium lining a gland-tubule; *f*, Pigmented connective-tissue cells; *g*, Focus of cartilage in connective tissue; *h*, Focus of cartilage in a gland-tubule. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 100 diameters.)

consists, at least in part, of tissues which do not normally occur at the site where the tumor is found.

As already mentioned, tumors containing cartilage frequently occur in the parotid and testicle, and similar tumors have been observed in other organs which normally contain no cartilage—e.g., in the breast and thyroid gland. Rhabdomyomata are found oftenest in the kidney, testicle, and uterus, and these organs have normally no striated muscle. Osteomata are sometimes found in intermuscular connective tissue and in the mucous membrane of the air-passages, at a distance from any part of the skeleton. The testicle is sometimes the seat of cystomata whose gland-tubules and cysts (Fig. 272) are lined with simple cubical (*b*) or cylindrical epithelium, in some parts stratified (*c*), in other parts provided with cilia (*d*), and in very rare cases also pigmented (*e*). These tumors may also contain foci of cartilage, which are usually found lying in the connective tissue (*g*), but may also, under certain circumstances, be found in the cystic cavities (*h*). Finally, the connective tissue also may contain pigment (*f*).

The cysts which are found in the neck also contain not infrequently cartilaginous foci in their walls, and sometimes also lymphadenoid tissue. In the sacral region congenital tumors are found which contain gland-tubules, as well as various sorts of connective-tissue formations.

These and many other similar appearances are very striking, and jus-

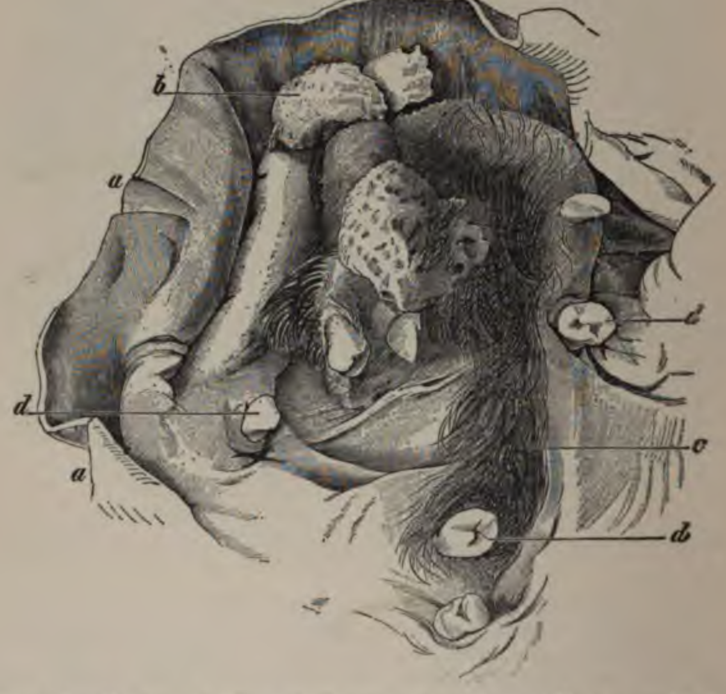

FIG. 273.—Portion of the wall of an ovarian dermoid cyst. *a*, Wall of the cyst; *b*, Projecting portion made up of fatty and cutaneous tissues; *c*, Hairs; *d*, Teeth. (Life size.)

tify us in giving such growths a special place among the tumors, and in classing them with the formations known as *teratomata*. But there are still other formations to which the term applies even more strongly, since in these are found not only different kinds of tissues, but even more or less complete organs, such as skin, hairs, nerves, muscles, bones, glands, rudimentary portions of intestine, etc.

Such structures are found oftenest in tumors which are known as **dermoid tumors** (Fig. 273)—that is, cystic tumors whose limiting membrane repeats more or less perfectly the structure of the skin, so that under stratified epidermis a corium with its papillæ is found, and often also, underlying this, a layer of subcutaneous adipose tissue. In many cases the membrane contains structures which are the special attributes of the skin, such as sweat and sebaceous glands and hair-follicles; and here and there locks of long blond hair are seen (Fig. 273, *c*). The cyst contains usually a fatty, unctuous material, the product of the epidermoid lining of the cyst, and in it fat, cast-off epithelial scales, and hairs are found.

Sometimes teeth (Fig. 273, *d*) are found here and there in the wall of the cyst. The specimens found are occasionally perfectly typical forms of teeth, and the base upon which they rest may be either connective tissue, bone, or cartilage. Other sorts of tissue-formations, such as nerves, muscles, and intestine, are very rarely found.

Dermoid cysts are oftenest found in the ovary, more rarely in the testicle, in the peritoneum, in the region of the base of the brain, in the neck, in the orbit, etc. Sometimes they are encountered in the shape of very small cysts not larger than a pea; but usually they are of considerable size—as large as the fist, or even, in some cases, as large as a man's head. In the ovary they are often associated with the formation of a cystoma. These growths plainly grow very slowly, and may be carried about for years and even for decades. When sufficiently large they may set up enough proliferative activity in the neighboring tissues to cause adhesions to take place between the tumor and neighboring organs.

Closely related to the dermoid cysts are the **hairy polyps** which are found in the mouth and pharynx, and which may inclose in their connective-tissue framework all sorts of tissue-formations. Of a similar nature, also, are the **cystic formations** which appear in the skin or under the skin in different portions of the body, but especially in the neck and in the median line of the back, and which are lined with stratified *squamous epithelium* (*dermatocysts*). These contain no hairs, but in the neck they are often combined with pathological new formations of cartilage.

Other growths which should also be reckoned among the teratomata are **cysts with cylindrical epithelium**, at times **ciliated**, which have been observed in the subcutaneous tissue, especially in the neck and the forehead, as well as within certain organs, and especially in the tissues of the peritoneum, in the subperitoneal tissue, and in the mediastinum.

Teratomata of a complicated structure—that is, those formations which with the dermoid cysts make up the real teratomata, in the narrower sense of the term—are most often found in the *sacral region;* but they likewise occur in other parts of the body, as, for instance, in the neck, in the face, and also in internal organs. They may be made up of the most diverse tissues: connective tissue, fat, cartilage, bone, muscle, peripheral nerves, central nerve-substance, cysts lined with epithelium, and tubular glands. Sometimes rudimentary or fairly well-developed organs, extremities, portions of backbone, intestine, nerves, portions of the central nervous system, etc., are also found in these formations.

§ 138. The formations described in § 137 can be explained only on the supposition that at the time of development **germinal fragments** have been misplaced, or else that **remains of fœtal formations** have persisted. The latter is the correct explanation for many cysts of the neck, and for those which occur in the peritoneal and subperitoneal regions, the testicle, and the mediastinum, where remains of the branchial clefts or of the fœtal urogenital apparatus have been preserved. The best explanation to give of all those formations which contain cysts or solid masses of tissue in places where such structures existed at no time of the development, is to consider them in the light of a transposition of tissues. It is an open question whether we have to do, in such cases, with autochthonous or with heterochthonous implantations—i.e., with monogerminal or with bigerminal implantations.

If a teratoma be found to contain very diverse tissue-formations which at least in part may be identified as representing rudiments of organs or perhaps even fully developed organs, which, however, are superfluous for the individual in whom they are found, we may consider such a tumor as a **heterochthonous teratoma** or as a **bigerminal implantation**—i.e., as a rudimentary twin which is more or less completely enveloped by the well-developed twin (cf. Double Monsters, § 157). On the other hand, if the teratoma contains only diverse tissues and cysts whose production does not necessarily imply the existence of a second individual, the tumor is to be looked upon as an **autochthonous teratoma** or as a **monogerminal implantation.**

The origin of a particular formation of tissue may be inferred from its structure, as a given tissue can be derived only from the same or a closely related tissue. Cartilage and bone indicate the presence of constituent portions of the skeleton, or more particularly of the respiratory apparatus. Striated muscular fibres can come only from the germs of the muscular system, and in the same manner nerve-tissues come only from some part of the peripheral or central nervous system. If gland-formations are present in whose structure we can recognize certain particular glands, we are sure of their origin, since they must have been derived from those glands.

The **cysts,** which so often represent teratoid formations, or form parts of teratoid tumors, may originate from various sources; and by means partly of the nature of the epithelium and partly of the site of the growth it is possible to determine their exact source of origin.

Cysts which are lined with stratified squamous epithelium, and whose walls present the same characteristics as the skin, must be regarded as *dermatocysts*, which spring from the ectoderm. Cysts with cylindrical and with ciliated epithelium, according to the site which they occupy, may have come from rudimentary gland-structures or from the medullary canal; and hence they may be divided into *adenocysts* and *myelocysts*. In the abdominal cavity cysts may arise from portions of the intestine which have become isolated through constriction, and similarly rudiments of the intestine which have developed from bigerminal implantations may change into cysts. These are called *enterocysts*. The pathological development of lymph-vessels in a cyst may lead to the formation of *lymph-cysts* lined with endothelium. Excessive dilatation of blood-vessels leads to the formation of *blood-cysts* or *hæmatocysts*.

The **transposition of the germs of tissues** in most cases can be inferred only from the structure of the resulting growth, while the mechanism of the original process cannot, as a rule, be made out. And yet there are also cases in which the changes are demonstrable. So, for example, in the cases where a hernia of the spinal cord in the sacral region returns to its proper place (von Recklinghausen), adipose (Fig. 274, *i*) and muscular tissues (Fig. 274, *k*) may find their way into the spinal canal and into the arachnoid space, and grow around the nerves. Arnold saw a transposition of adipose, cartilaginous, glandular, and glial tissues at the lower end of the trunk of the body, in a case of myelocyst with complete defect of the lumbar, sacral, and coccygeal portions of the spinal column.

If a tissue is transplanted it may remain unchanged, or gradually be destroyed in its abnormal situation and its place be taken by other tissue. Or *from this transplanted tissue, by further growth, a heterotopic tumor may develop.* According to the observation of various authors (Arnold, Balin, Lesage, Legrand, Bird, von Bergmann, Maas, Ziegler, and others), it cannot be doubted that lipomata, fibromata, dermoid cysts, and hairy polyps may arise within the cavities of the skull and vertebral column, as a result of the retrogression of clefts and hernias in these parts.

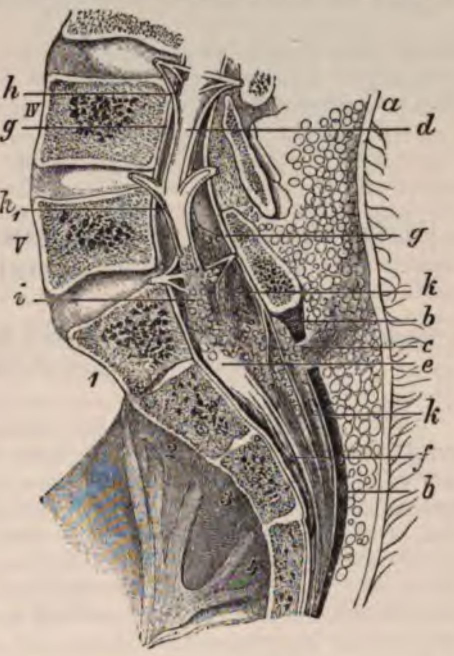

FIG. 274.—Spina bifida occulta, with myolipoma inside the vertebral canal. (Sagittal section about 1 cm. to the left of the median line. Reduced about one half. Copied from von Recklinghausen.) *a*, Abnormally hairy skin; *b*, Fibrous covering which forms the posterior wall of the sacral canal, with a slit-like opening at *c*; *d*, Spinal cord; *e*, Conus medullaris, lying in the second sacral vertebra (2) instead of in the second lumbar vertebra; *f*, Cauda equina; *g*, Dura mater; *h*, h_1, Recurrent left anterior nerve-roots of the third and fourth lumbar nerves; *i*, Fat; *k*, Muscular tissue; IV, Fourth, and V, fifth lumbar vertebræ; 1-4, Sacral vertebræ.

Accessory suprarenal capsules, whether lying within the kidneys or elsewhere—e.g., in the broad ligaments (Marchand)—may not only persist, but may form the starting-point for various tumor-formations. In the same way tumors may develop in supernumerary (*abgesprengten*) thyroid or mammary glands. A cancerous growth has often been observed to start in branchiogenic cysts; and from isolated portions of the rudimentary epithelial dental membrane not only dental cysts but malignant tumors (cancers) may arise.

SECTION VIII.

Disturbances of Development and the Resulting Malformations.

I. General Considerations in regard to Disturbances of Development and the Origin of Malformations.

§ 139. After the union of the sexual elements has taken place, the development of the embryo progresses by a continual division of nuclei and cells. Along with this division there arise in an orderly manner special groupings and differentiations of the cells, leading to the formation of special tissues and organs. The cell-proliferation, as well as the development of the individual cell-groups into special organs and parts of the body, depends upon internal causes, and is controlled by characteristics which the embryo has received by transfer of inheritable paternal or maternal characteristics which were in the ascendant at the moment of the union of the sexual elements, which are to be regarded as the carriers of inherited characteristics. It follows that not only the characteristics proper to the species, but also the special peculiarities of the individual, are predetermined in the germ, and the development of the embryo proceeds essentially under the control of self-contained moulding forces. And yet this development is not accomplished without an influence from the environment, in that the embryo of necessity receives nourishment and warmth from the maternal organism, and is exposed to mechanical influences on the part of its envelopes and the uterus. These influences may operate to modify the development of the fœtus.

In every species of animal, man included, the bodily form and the shape of the organs present a *particular type*, which experience has shown recurs continually, and which is therefore looked upon as *normal*. If there are departures, more or less marked, from this type, which are to be referred to an abnormal course of the intra-uterine development, the condition is called a **congenital malformation.** If the departure from the normal build is very great, so that the affected individual is grossly misformed, it is spoken of as a **monster.**

It is customary to use the term malformation to designate only such anomalies in the form of the whole body or individual parts of it as present to a mere external inspection rather striking departures from the normal. It is nevertheless entirely correct to use this term for pathological conditions of intra-uterine origin, which consist not so much in an abnormal change in form, but rather in a partial or faulty organization of the affected part or organ.

A **single malformation** is one which originates from a single individual, while a **double malformation** or a **double monster** is one which is made up from two individuals.

Malformations may arise in two ways: from internal causes and from external causes.

As **internal causes** may be reckoned all such as already exist in the germ, so that in the development of the embryo abnormal forms arise spontaneously, without intervention from without. When such a malformation occurs for the first time in a family it must be regarded as a *primary germ-variation.* This is to be regarded in either of two ways: there may have been an abnormality of one or the other of the sexual nuclei which entered into union, or they may both have been normal, but from their union a variety has arisen which from our point of view is to be looked upon as pathological (cf. § 32). It is also possible that disturbances in the process of fecundation can give rise to pathological variations.

If a similar malformation has already occurred in a parent, the case may be one in which the defect has been *inherited.* If a malformation which has appeared is a peculiarity which was not present in one of the parents, but did occur in remoter ancestors, while it was wanting in the intermediate links, the occurrence is spoken of as *atavism.*

As primary germ-variations we find the very same malformations that occur by inheritance; in other words, only those malformations are inherited that have originally presented themselves as primary germ-variations. To these malformations that may be transmitted by inheritance belong an increase in the number of fingers or toes (polydactylism), pigment spots of the skin, abnormal hairiness, harelip, and certain pathological conditions of the nervous system, as, for example, fibromata of the peripheral nerves.

Under **external causes** of malformations the first to be considered are *jarrings, pressure,* and *disturbances in the supply of oxygen and nourishment.*

Jarrings of the uterus can very likely directly damage the egg at an early stage. At a later stage in the development of the embryo the damage worked by trauma is probably more often to be looked upon as the result of a tearing loose of the egg and bleeding from the decidua, leading to malnutrition of the egg. It is evident that bleeding from other causes, changes in and contaminations of the maternal blood, as they occur in infectious diseases, also disease of the uterus itself, will have a detrimental effect on the developing egg; yet all of these conditions probably lead more often to the death of the fœtus and to extrusion of the egg than to the development of a malformation. Infectious diseases of the mother may be transmitted to the fœtus and cause there characteristic disturbances. An abnormal pressure from the uterus or the membranes may be exerted upon the embryo, especially where the amniotic fluid is in small quantity. Deformities of the extremities—as, for example, club-foot, flat-foot, and club-hand—not rarely show signs of pressure having been exerted (Fig. 278).

From the anatomical appearances in some malformations it appears that **pathological conditions of the amnion** are particularly likely to exert a damaging influence on the embryo. The amnion is formed at the time when the embryo sinks into the yolk which is then lying under it, and arises from the extra-embryonic portion of the somatopleure, which forms folds anteriorly, posteriorly, and laterally, and surrounds the embryo. From the coalescence of these folds over the dorsum of the embryo the latter comes to be in a cavity, whose envelope, the amnion, is con-

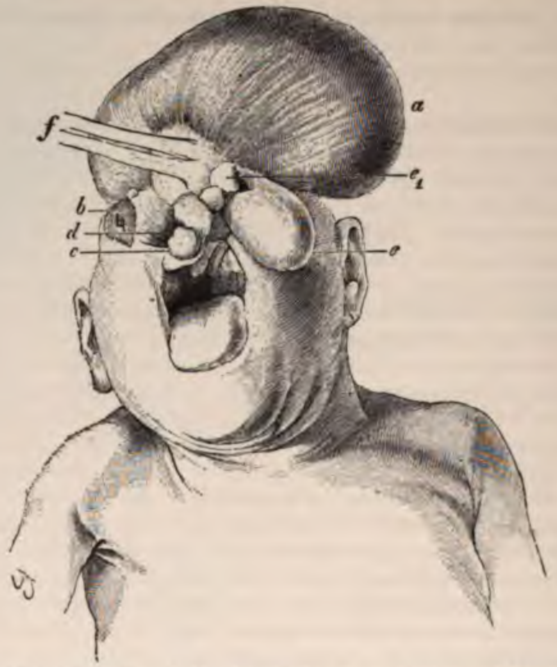

FIG. 275.—Malformation of the head, due to adhesions of the membranes to the frontal region (close adhesions of the placenta to the uterus). *a*, Cutaneous sac inclosing a vascular, spongy tissue containing abundant cysts; *b*, Eye; *c*, Distorted lip; *d*, Funnel-shaped depression lined with mucous membrane; *e*, Right, e_1, left ala nasi; *f*, Fibrous bands. (Reduced to three-fourths natural size.)

nected with the embryo at the umbilicus. The amniotic sac contains at first but little fluid, which later increases in amount.

A disturbance of embryonic development may arise from *abnormal adhesions between the embryo and the amnion*, and also from *pressure of the amnion upon the embryo*, this pressure being due to insufficient dilatation of the amniotic cavity. Adhesions are not rarely demonstrable even at the birth of the child,

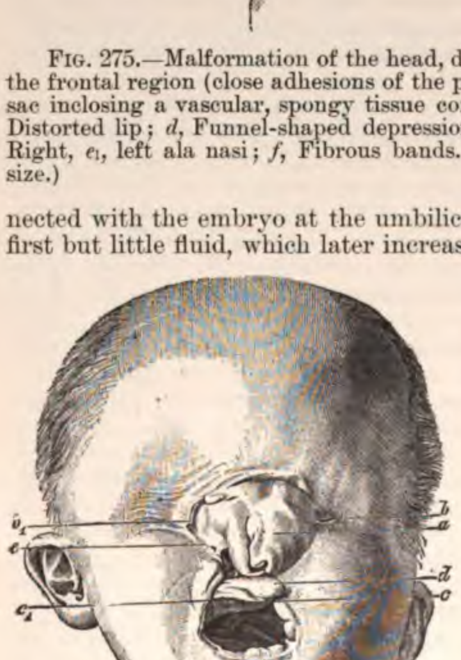

FIG. 276.—Malformation of the face, caused by amniotic adhesions and pressure (asymmetry of the face). *a*, Misshapen nose; *b*, b_1, Rudimentary openings between the eyelids; *c*, c_1, Clefts in the upper lip and alveolar process of the upper jaw; *d*, Intermaxillary bone with prominent lip; *e*, Oblique facial fissure, closed so as to make a furrow by scar-tissues.

being found as connecting bands and threads (Figs. 275, *f*, and 276); and their relations to the malformed portions leave no doubt that they stand in causal relation to the malformation. Such adhesions may cause grave malformations of the cranial (Fig. 275) or of the facial (Fig. 276) portions of the skull. Not infrequently portions of extremities are snared off by amniotic threads (Fig. 277).

How far these attachments of the amnion to the fœtus are to be referred to primary adhesion and union, and how far to inflammatory processes appearing later, is still the subject of controversy. If a portion of an extremity—for example, a finger—is caught in a loop of such a uniting band, and then the band put on the stretch by accumulation of the amniotic fluid, the portion included in the loop will be snared (Fig. 277) and eventually amputated. At an early embryonic period amputated portions may be absorbed.

What gross deformities may appear on the head as a result of amniotic adhesions is shown in Figs. 275 and 276, and from these cases it may readily be inferred what the effect of adhesions on other parts of the head may be. It is not rare at birth to find adhesions no longer apparent, and only a scar-like appearance to mark the affected spot (Fig. 276).

According to Dareste and Geoffroy-St. Hilaire, an abnormal snugness of the amnion exerts also a damaging influence on the embryo. So it is also claimed that abnormal tightness of the cephalic cap of the amnion is capable of causing the malformations known as anencephalia and exencephalia (§ 145), cyclopia (§ 146), and cebocephalia or arrhinencephalia

Fig. 277.

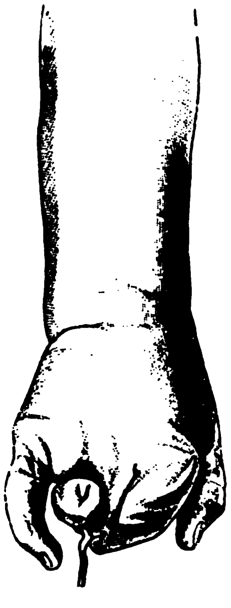

Fig. 278.

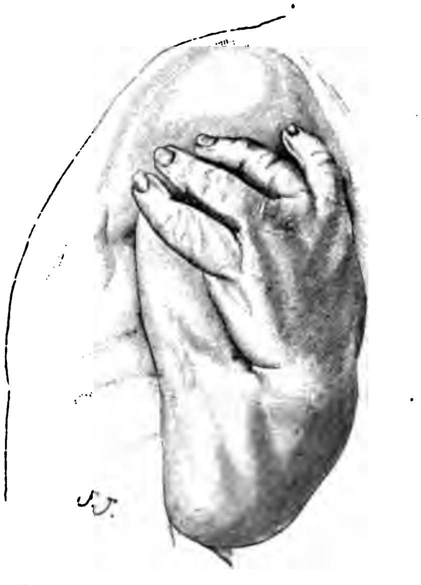

FIG. 277.—A hand stunted by amniotic adhesions; ring-finger snared off; middle and index fingers grown together and distorted. (Reduced one sixth.)

FIG. 278.—A hand stunted and misshapen by pressure; thumb wanting; hand flattened; great bending and shortening of the forearm. (Reduced one fifth.)

(§ 146); while abnormal tightness of the caudal cap leads to stunted development of the lower extremities (§ 150). Marchand refers also phocomelia to pressure exerted at an early period. Finally, clefts which occur in the anterior abdominal and thoracic walls (§ 148) are associated with a deficient growth of the amnion; still the latter condition is often not so much the cause as it is a concomitant of the malformation, which may follow from a variety of causes, but is doubtless often to be classed with the spontaneous or primary malformations.

The period at which the damaging influences exert themselves naturally varies much, and so, also, does the extent of the damage. The earlier the damage occurs the more extensive it generally is. Malformations in the more restricted sense arise mostly in the first three months, a period when the body and its individual parts are assuming their proper forms. Damage to the fœtus at a later period occasions *departures which in appearance are more nearly allied to those acquired after birth.*

Some malformations are **typical**—that is to say, they always reappear in the same form; while others, again, are entirely **atypical**, so that often the most astonishing anomalies of form arise. The latter are mostly the result of harmful influences operating secondarily from without, while the former may be regarded as chiefly due to internal causes. External influences, however, may also cause typical deformities.

The damaging influences which affect the normally constituted embryo in the process of development play in the etiology of malformations a more prominent rôle than inheritance or primary germ-variation. This comes about from the general use of the term malformation in the sense only of gross anatomical departures, such as arise through external causes; while the pathological peculiarities which pass by inheritance from the parents to the child, and the primary germ-variations, manifest themselves much less by changes in the outward form than by deficient or perverted function of the tissues or predisposition to diseases, etc.—departures whose anatomical basis can be found only by painstaking study, or is wholly insusceptible of anatomical demonstration.

Geoffroy-St. Hilaire * discards entirely the teaching of primary abnormality of the germ (Haller and Winslow), and attributes arrests of development simply to mechanical influences. Panum † agrees with him in general, although he admits the possibility of a primary abnormality. In hens' eggs he produced malformations by temperature variations of the incubator, and also by varnishing the shells. Dareste ‡ made similar experiments, and produced deformities due to arrests of development by setting the eggs on end, by varnishing the shells, by raising the temperature above 45° C., and also by irregular warming of the eggs.

Very recently L. Gerlach, Fol, Warynsky, Richter, Roux, and Schultze have experimented in this direction, and have sought, with some success, to produce malformations in hen embryos by localized influence of radiant heat, variations of temperature, varnishing the eggs, changes of position, injuries, removal of a portion of the white of the egg, and by agitation. Roux, experimenting on frogs' eggs, found that, after destruction of one of the divisions formed by the primitive streak, the other continued its development to the formation of half an embryo, demonstrating that the portion on either side of the primitive streak contains within itself the developmental power to form the corresponding half of the body. But the body-half which is wanting may be later replaced by subsequent development from the undestroyed half, and a whole structure be produced, showing that a half contains powers to produce also the other half.

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* "Hist. gén. et partic. des anomalies de l'organisation chez l'homme et les animaux," Paris, 1832–37.

† "Untersuch. über die Entstehung der Missbildungen," Berlin, 1860.

‡ "Recherches sur la production artificielle des monstruosités," Paris, 1877.

Schultze experimented on the eggs of amphibia. They normally assume a position in which the darkly pigmented protoplasm of lighter specific gravity lies above, and the heavier clear protoplasm, rich in yolk granules, lies below. Malformations may be produced by placing the eggs in an abnormal position and preventing their resuming the normal position; and the degree of malformation stands in direct relation to the size of the angle which the attraction of gravity makes with the abnormally placed axis of the egg. By turning the egg through an angle of 180° in the two-cell stage a double monster is regularly produced. By the same turning in the eight-cell stage, development is completely stopped. All this shows that gravity is another influence capable of causing disturbances of development, and that these disturbances arise from displacements consequent upon a sinking of the heavier and a rising of the lighter constituents of the egg.

For the production of a malformation, it is manifest that the damage to the embryo must not be too severe; otherwise the embryo will die. Above all, the activity of the circulatory apparatus must be preserved. If the embryo dies, it is either expelled from the uterus together with the membranes, or it is absorbed while the membranes continue for a time their development. A malformed fœtus cannot sink below a certain minimum of development without perishing at an early period, unless maintained as a sort of parasite upon another fœtus developing at the same time (cf. § 157).

§ 140. **Single malformations** may conveniently be divided, according to the sort of departure which characterizes them, into five groups.

As **arrests of development**, or **monsters due to defective development**, are classed all those malformations in which the whole or a part of the body is abnormally small and poorly developed (*hypoplasia*), and also the malformations characterized by absence or very great dwarfing (*agenesia*, *aplasia*) of individual organs or parts of the body. In this class belong absence of the brain or parts of it, or abnormal smallness of the brain; defects in the septa of the heart; absence and dwarfing of the extremities, etc.

Where parts of the body or organs are normally formed by the union of distinct centres of development, and by a primary or secondary arrest of development this union fails to take place, arrests of development may show themselves as *clefts* and *reduplications*. Thus imperfect development of the plates forming the anterior body-wall gives rise to clefts in the median line of the thorax and abdomen; failure of the maxillary processes of the first branchial arch to unite or to form a union with the intermaxillary process gives rise to clefts in the facial portion of the head. If the lateral halves of the early spinal cord fail to unite, a duplex cord results. Deficient union of the early lateral halves of the female genital tract results in more or less extensive duplication of the uterus or vagina.

Where at an early stage the beginnings of two organs lie in proximity, they may unite so as to produce a *coalescence* or *adhesion* between two organs or parts normally distinct. So it may happen that the kidneys are more or less united, and the eyes may be more or less completely merged into a single organ. Such mergings of organs arise in two ways: from secondary union of divided organs, or from deficient separation of two organs which develop from a single focus.

Malformations due to excessive growth, or **monsters due to excessive development**, are characterized sometimes by the *abnormal size* of individual parts, sometimes by *multiplication* of their number. An extremity or a portion of a finger may attain an abnormal size (*partial giant growth*), or the whole body may be included in the abnormal growth (*general giant *growth*). These are examples of increase in size of members. A multiplication of the number of parts occurs notably in the glands of the breast, the spleen, the suprarenal capsules, and the fingers. The *supernumerary organs* or members are mostly smaller than the normal ones.

Malformations occur, also, through an **abnormal disposition of parts** (*monstra per fabricam alienam*). Under this head are included certain anomalies of the thoracic and abdominal organs which are characterized by abnormal positions of the organs, and also in part by the changes in relations between individual parts. In this class belongs the transposition of the organs of the thorax or abdomen, or of both at the same time (*situs transversus*). Various cases of defective formation in the heart and great vascular trunks may also be classed here, though more properly the instances of transposition of the vascular trunks should be reckoned under arrests of development.

A fourth group of malformations is caused by the presence of **tissues in unusual situations** and the **persistence of fœtal structures**, as already spoken of in §§ 137 and 138.

Finally, a fifth group includes malformations exhibiting **a mixture of the sexual characteristics**, subdivided into *true and false hermaphrodites*. True hermaphrodites possess both a male and a female generative gland. False hermaphrodites are unisexual, but the remainder of the sexual apparatus does not correspond to the generative gland, or there is a simultaneous formation of organs belonging both to the male and to the female. A part of these malformations are arrests of development; others are to be regarded as cases where from the original bisexual embryonic formation the organs of both sexes have attained development, whereas normally the structures characteristic of one sex, instead of developing, dwindle away and persist only in a very rudimentary form.

§ 141. **Double monsters** (*monstra duplicia*) are instances of a duplication of the whole body or of parts of the body. The twins are always of the same sex, and are mostly united together at corresponding parts of the body. The duplicated parts exhibit sometimes equal, sometimes unequal development; in the latter case one of the parts is dwarfed and appears as a parasitic appendage to the well-developed individual. This permits a subdivision into an **equal** and an **unequal form of double monster.**

According to the older theories, double monsters arose from a growing together of two embryos in the uterus (Meckel, Gurlt, Geoffroy-St. Hilaire). It was indeed supposed that where there were two separate and distinct eggs the membranes might disappear at the point of contact and then the two fœtuses blend. This view is now abandoned.

All double monsters come from a **single** *egg, and develop from a single germinal vesicle.*

According to Kölliker, the first evidence of embryonic development appears as a white, circular, opaque spot, the embryonic area. The ectoderm of the bilaminar blastodermic vesicle becomes thickened by enlargement of the cells, and forms this embryonic area. Later, the embryonic area takes on a pyriform shape. Its posterior and sharper extremity becomes rounded and thickened and drawn out into a wedge-shaped appendage. This is the earliest trace of the primitive streak, and consists of a thickening of the ectoderm at the same place where the mesoblast is also found, and spreads itself out between ectoderm and entoderm over the e embryonic area. After the primitive streak has been present in the embryonic area, the medullary groove forms in front the same time the embryonic area becomes differentiated into portion about the medullary groove and an outer lateral por- e various parts of the body are formed by the progressive de- t of these two portions.

al views of the origin of double monsters may be entertained. may be supposed that two embryonic areas arise in the wall of blastodermic vesicle, which grow, impinge one on the other, and a greater or less extent. A second possibility is the formation single embryonic area of two primitive streaks and two medul- ooves, which either remain separate or partially merge one into r. A third case would be where the primitive streak was single, e medullary groove was double either in a part or in the whole of ent. Finally, it may be that a duplication takes place at a later of development, and then affects only individual parts.

all of the above possible modes of duplication the duplication place by a double formation, at a certain stage in development, of rt that is normally single. In the first instance the duplication dates the period of formation of the embryonic area; in the rest it begins in the embryonic area. In the first three instances it affects the struc- s in the body-axis, in the fourth it is confined to such as do not lie the body-axis.

To explain the formation of double monsters it is essential to suppose duplication of parts of the blastodermic vesicle or of the embryonic ea. The only question is how far it may be possible for a doubling at has already taken place to disappear by a subsequent blending. hus, if there are two entirely distinct embryonic areas, it may be asked whether only separate homologous twins can arise, or whether a merg- ng can take place at an early stage. This question cannot be definitely settled at present. There is, however, every likelihood that embryonic areas in process of formation may merge one into another. About the causes of duplication of the embryonic elements in the blastodermic vesicle we have thus far no knowledge. According to Fol, double and multiple monsters arise from anomalous impregnation of the ovum by two, three, or more spermatozoa; but other observations (Born) tend to show that ova impregnated by two or more spermatozoa do not develop at all.

The views of the authors as to the formation of double monsters vary greatly. Some (Förster, Virchow, Oellacher, Ahlfeld, and Gerlach) advocate the theory of a division. Others (Schultze, Panum) hold that more or less completely divided elements reunite. According to Rauber, two or more primitive streaks arise in one embryonic area, and later come in contact at some point and merge more or less one into the other. This is called the theory of radiation. Marchand holds that generally two embryonic germs are formed, and that they blend together. The duplication, according to him, is referable to conditions existing before the beginning of the medullary groove—that is, to conditions of the ovum itself, or of its impregnation, by which there are preformed two distinct centres for the formation of medullary grooves.

Born has noted that those fish eggs which develop into double formations produce a normal and single first furrow, exactly like those from which a single embryo springs. Probably the second furrow runs as it does in the ordinary eggs. As in the ordinary egg the first furrow divides the germinal material into a right and a left, or an anterior and a posterior half (Roux), it follows that in those eggs destined to develop into double formations the first division must have another significance. Probably a full half of the qualities of the mother-germ pass in congruent arrangement into each of the halves, and the division into right and left, or anterior and posterior, does not take place until the second division occurs. In most of the double monsters among the fishes, more or less of the posterior portion of the body is single; which gives color to the theory that between the two plans in accordance with which the first division can take place, there must be something like an intermediate plan, in accordance with which one part of the nuclear material subdivides in a congruent manner, while the other subdivides differently.

Eggs which show a primary threefold or a quadruple division—in which probably an excessive impregnation has taken place—perish.

In recent years successful experiments have been made in the production of double monsters from the eggs of animals. They were conducted by Gerlach, O. Schultze, and Born. Gerlach produced double monsters (anterior duplication) from hens' eggs by varnishing them before incubating, and leaving only a V-shaped spot in the region of the primitive streak free. Schultze produced double monsters by turning frogs' eggs through an angle of 180° (cf. § 139). Born succeeded in uniting together portions of the larvæ of amphibia, not only of the same kind, but also of different species and families (rana esculenta with bombinato rigneus and with triton). From all these experiments the conclusion may with certainty be drawn that double formations may be produced from a normally constituted egg through secondary influences, and that neighboring embryonic elements may merge and grow one into the other.

II. Special Malformations in Man.

1. *Arrests of Development in a Single Individual.*

(*a*) *Arrest in the Development of all the Embryonic Elements.*

§ 142. Arrest in the development of all the embryonic elements manifests itself in two ways. If the disturbance is very marked, further development becomes impossible, and the embryo either dies at once or it becomes stunted and after a certain time perishes. If the disturbance is not so great a normally formed fœtus develops, but it remains small and weakly.

When a fœtus dies it remains unchanged only for a short time; sooner or later it undergoes various changes. In the majority of cases it is expelled from the uterus along with its membranes (**abortion**). In the earliest periods of development the **embryo may disappear by absorption.** The fate of the membranes in this case varies. Usually they are expelled; in some cases they remain and undergo various changes. Most frequently they form **flesh-**, **thrombus-**, or **blood-moles**—fleshy masses consisting of the membranes and blood-clots. The clots form the chief bulk, come from the placenta materna, and are often the cause of the death of the fœtus.

The chorionic villi may degenerate in a peculiar manner, then grow and produce club-shaped and globular, bladder-like, translucent structures (Fig. 279), which give the egg the appearance of a bunch of grapes, and furnish a warrant for the name by which it is known—**grape-cluster mole.** The little sacs have a diameter of from two to twelve or more millimetres, and hang from slender stems, which are attached to other sacs or directly to the chorion. Their tissue consists of myxomatous tissue with few cells and fibres, which are separated by greater or less quantities of mucilaginous fluid.

The death of a fœtus in an advanced stage of development results, provided it be not expelled, in the formation of a **lithopædion.** This occurs most frequently in cases of extra-uterine pregnancy, where the fœtus occupies an abnormal site, as in the peritoneal cavity, in a Fallopian tube, or in an ovary. If a fœtus so placed dies at such an advanced state of development that it cannot be absorbed, it may be carried in the maternal organism for years. Not infrequently its form is perfectly retained (Fig. 280), and the whole fœtus becomes enshrouded in an envelope of connective tissue. In other cases the fœtus, in the course of time, becomes converted into a partially fluid mass, which contains the osseous remains, as well as fat, cholesterin, and pigment, and is inclosed in a fibrous capsule. Usually lime-salts are deposited in the new-formed capsule, as well as in the fœtal elements that remain.

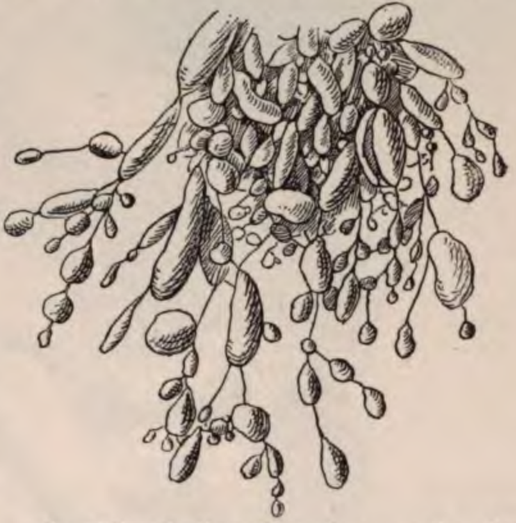

FIG. 279.—Portion of a mole, presenting the form of a bunch of grapes. (Natural size.)

All of these forms are included in the term lithopædion, but they are subdivided under three heads (Küchenmeister). The fœtus may be mummified, but easily shelled out from calcified membranes (*lithocelyphos*). Or the fœtus, while yet alive, may become adherent at a number of points with the membranes, and later these points become calcified, while the remaining parts undergo mummification (*lithocelyphopædion*). Or, again, the membranes may rupture and the fœtus be discharged free into the peritoneal cavity, and later become incrusted with lime-salts (*lithopædion* in the narrower sense).

A second form of general arrest of development shows itself in **dwarf-growth**—that is, a general diminution in the size of the body (*microsomia* or *nanosomia*). Sometimes the proportion between individual parts is not maintained, and the head especially is sometimes disproportionately large.

According to observations of His, an embryo may for one reason or another come to a standstill in its development, and yet be retained for weeks or even months in its envelopes. The first change that takes place at the approach of death is a great swelling of the central nervous system, which leads to deformities of the head. Later, the tissues become infiltrated with wandering cells, which make the boundaries between the organs vague. The whole embryo becomes soft and dark, and the superficial configuration of the body may become indistinct.

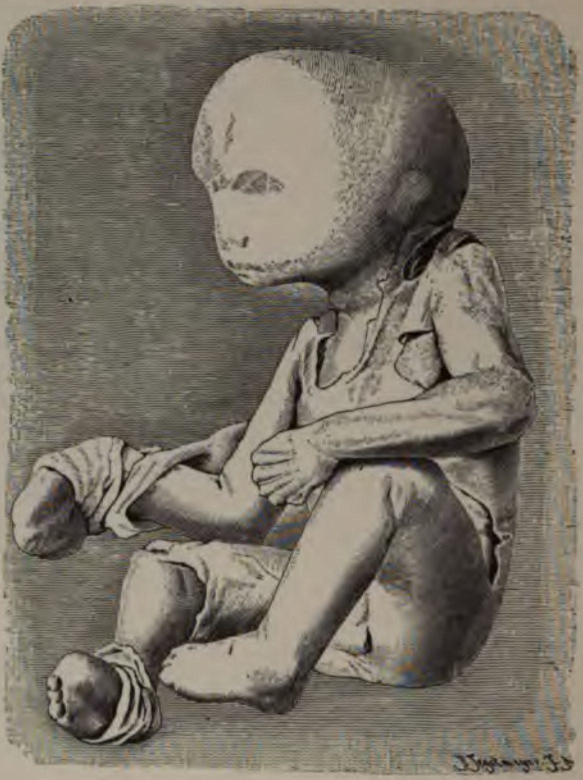

FIG. 280.—Fœtus entirely inclosed in fibrous membranes. (Removed from abdominal cavity by operation two years after beginning of pregnancy.) Extra-uterine pregnancy caused by embryo breaking through uterine end of a Fallopian tube into abdominal cavity. (Reduced one third.)

(*b*) *Deficient Closure of the Cerebrospinal Canal and the Accompanying Malformations of the Nervous System.*

§ 143. The **spinal column** originates from bilateral halves, and it is only by the union of these that the spinal canal is formed. If for any reason this union fails to take place, there arises the condition known as **rachischisis.**

Where closure of the canal fails throughout its entire length the condition is called *rachischisis totalis* or *holorachischisis* (Fig. 281). The vertebræ form a shallow furrow posteriorly, covered in the main only by a thin, transparent membrane, though rarely rudiments of the spinal cord may show as whitish bands and lines.

The delicate envelope which lies in the furrow and covers the dura mater lining the bones, is the ventral portion of the pia mater spinalis. In the lateral portions there may usually be seen in the pia whitish bands which represent the ligamentum denticulatum. More or less extensive rudiments of the nerve-roots may have formed; in which case they will be seen lying beneath the pia and dura mater. They are in general less

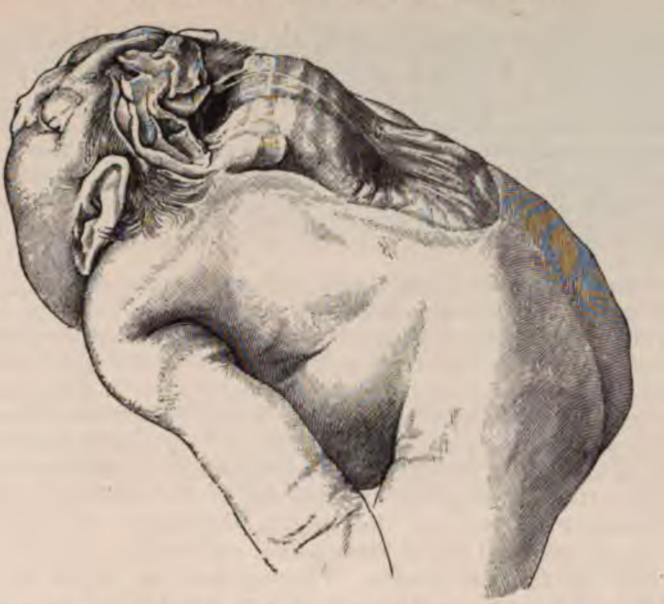

FIG. 281.—Craniorachischisis, with total absence of the brain and spinal cord. The skull is covered by irregular skin-like masses, the spinal furrow with a delicate envelope (pia mater). Under this envelope, in the lowest portion of the spinal furrow, a few whitish lines are to be seen. Kypholordotic bending and shortening of the spinal column. (Reduced one sixth.)

well marked in proportion to the smoothness and thinness of the pia mater and the paucity of spinal cord rudiments. Of the arachnoid there are usually present only scattered threads and bits of membrane spread out between the pia and the dura mater.

A *partial rachischisis* (*merorachischisis*) is far more frequent than the total variety, and affects mostly the sacrolumbar or less often the upper cervical portion of the spine. The intervening portion is seldom affected. The dorsal sur-

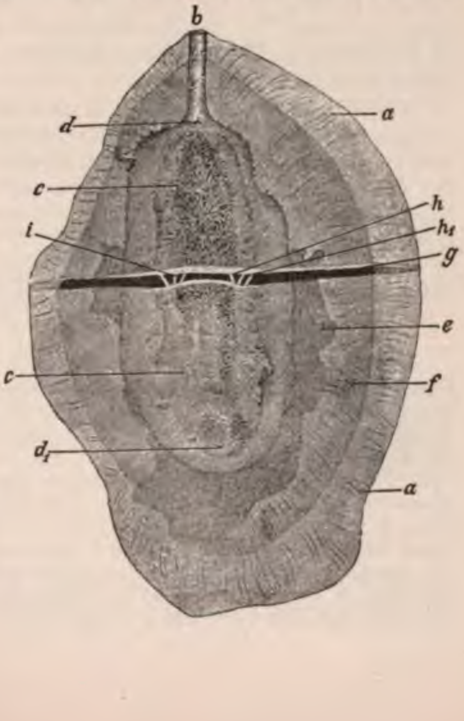

FIG. 282.—Rachischisis partialis. (After von Recklinghausen.) *a*, Outer skin with hairs; *b*, Spinal cord, laid bare by dissection; *c*, Area medullo-vasculosa; *d*, Cranial, d_1, caudal polar furrow; *e*, Zona epithelo-serosa; *f*, Zona dermatica with hairs; *g*, Space between dura mater and pia; *h*, Anterior, h_1, posterior nerve-roots; *i*, Ligamentum denticulatum.

face of the vertebral bodies whose arches have remained rudimentary is mostly covered by a mass of velvety red tissue (Fig. 282, *c*) (von Recklinghausen) closed in by a delicate integument; though the amount of this tissue may be very small, or may even be wanting. External to this tissue-mass, which is not everywhere equally abundant, and which decreases at the sides, comes usually a delicate, transparent, vascular skin (Fig. 282, *e*); next, a zone of skin with an epidermis, but somewhat thinner than the normal skin, and often bearing abundant hairs (Fig. 282, *f*); then, finally, comes the normal skin.

According to von Recklinghausen, the soft red tissue-mass (*c*) lying in the median line is the rudiment of the malformed spinal cord, and is an extremely vascular tissue, containing often more or less abundant parts of the spinal cord, as nerve-fibres, ganglion-cells, and glia-cells, and is therefore appropriately called *area medullo-vasculosa* (von Recklinghausen).

The area medullo-vasculosa is sometimes a continuous tissue; sometimes it is scattered in patches and bands, and forms only a delicate web. The cranial as well as the caudal extremity of this median area may end in a distinct furrow, designated respectively as the *cranial* and the *caudal polar furrow* (*Polgrube*—von Recklinghausen) (d, d_1). Ventrally this is next to the spinal cord (b); in lumbosacral rachischisis caudally it is connected with the filum terminale. The tegument on which the area lies is only the pia mater, which also continues into the red zone spoken of above (e), which, being covered also with epithelium, is designated as the *zona epithelo-serosa* (von Recklinghausen). The prominent zone bordering this and covering the rudiments of the posterior vertebral arches (f) is formed of cutis and is known as the *zona dermatica*.

On the ventral side of the pia mater that forms the covering of the defect is a cavity (g), bounded on its deeper side by the dura mater and the external layer of the arachnoid; so that this space is in reality the ventral portion of the subarachnoid space, and, as is normal with this space, is crossed by the ligamentum denticulatum (i) and the nerve-roots (h, h_1), which, in the region of the area medullo-vasculosa, lose themselves in the pia-like tissue.

The *origin of rachischisis* is ascribed by authors to various causes: accumulation of fluid within the vertebral canal; pressure from without and infolding of embryonic membranes; and faulty separation between the neural canal and the epidermal layer of the skin. According to von Recklinghausen, the fault lies in agenesia or hypoplasia of the dorsal ridges from which the vertebral arches are to be formed, and the malformation of the spinal cord is also to be referred to the earliest embryonic period, being due to under-development of the blastoderm. The defects of skin, muscles, and fasciæ are attributed to the same cause.

In the earliest embryonic period the medullary groove is formed by the throwing up on either side of the median line of wall-like eminences. The neural canal is formed by a converging growth of these and their uniting posteriorly. These masses of cells lying by the side of the canal develop into an envelope which surrounds the neural canal and forms at first a membranous and not articulated vertebral column. In this arise, in the beginning of the second month, discrete cartilages, from which in the further course of development the vertebral bodies and arches are formed, while between them are developed the intervertebral disks and ligaments. The cartilaginous vertebræ are not complete until some time in the fourth month, and until this time the dorsal covering of the neural canal is formed by the membranous vertebral column. The cartilaginous vertebræ are replaced by bone in the course of development.

The spinal cord and the brain are formed from the medullary tube. The portion that is to form the brain changes at an early period into three vesicles. The anterior of these, the forebrain, develops laterally the eye-vesicles. The middle portion grows forward and upward, dividing into the first secondary vesicle and the second secondary vesicle. From the first secondary vesicle arise the cerebral hemispheres, the corpora striata, the corpus callosum, and the fornix. From the second secondary vesicle arise the optic thalami and the floor of the third ventricle. The middle primary vesicle, or midbrain, forms the corpora quadrigemina, while the third differentiates into a fourth and a fifth secondary vesicle, from which are developed respectively the pons and cerebellum, and the medulla oblongata.

The cerebral portion of the neural canal is inclosed in the prevertebral plates of the head. These make the primordial membranous skull, whose basal portions become cartilage in the second month of fœtal life. In the third month the absal cartilages and also the membranous vault begin to ossify.

§ 144. If fluid accumulates in the subarachnoid space in a case of partial rachischisis, provided the pia mater is intact and does not allow of its escape, this membrane is made to protrude posteriorly in the form of a globular tumor, known as a **myelomeningocele** (Fig. 284). Frequently these cases are included under the head of **spina bifida**, a characterization in general use for all those cases in which a hernia-like tumor projects through a defect in the vertebral canal (Fig. 283). In harmony with its mode of formation, the myelomeningocele may be capped by an area medullo-vasculosa (Fig. 284, *c*); but this may be entirely wanting, or reduced to little scattered patches of vascular tissue. The skin of the neighborhood extends from the sides more or less ex-

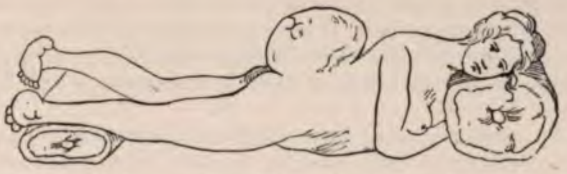

FIG. 283.—Spina bifida sacralis. (After Froriep and Förster.) Girl of nineteen years, born with a tumor the size of a pigeon's egg over the upper sacral and lower lumbar regions, which enlarged from the sixth year on, while at the same time club-feet developed.

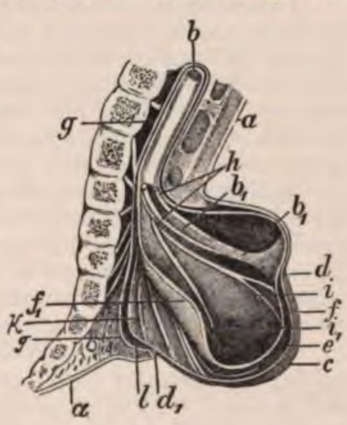

FIG. 284.—Myelomeningocele sacralis in sagittal section, a little to the left of the median line. (After von Recklinghausen.) *a*, Skin; *b*, Spinal cord; b_1, Column of the cord; *c*, Area medullo-vasculosa; *d*, Cranial, d_1, caudal polar groove; *e*, Pia mater; *f*, Arachnoid, somewhat separated from the pia mater; f_1, Portion of the pia mater turned over; *g*, Dura mater; *h*, Recurrent roots of the fourth lumbar nerves; *i*, Radix anterior, i_1, radix posterior of the fifth lumbar nerve, running free in the arachnoid sac; *k*, Sacral nerve-roots between the arachnoid and pia; *l*, Filum terminale.

tensively on to the walls of the tumor. The dura mater is never present on the dorsal portion of the tumor. By the elevation of the deformed region the spinal cord (b) is pulled outward posteriorly (b_1). The nerve-roots pass in part through the cavity of the sac (i, i_1), in part they are attached to its wall, and run there between the pia and the arachnoid. Occasionally, also, a nerve (h) may spring from the column of the cord as it courses through the sac.

In virtue of the fact that the sac is formed by an accumulation of fluid in the subarachnoid space, it is called a *hydromeningocele* or a *hydrorachis externa circumscripta;* but inasmuch as the spinal cord is pressed outward and protrudes, the condition is also spoken of as a *myelocele*, and it is customary to designate the whole condition as a *myelomeningocele.*

If there be a deficiency of the bony wall of the vertebral column at some point, and the dura mater be there abnormally yielding, a localized accumulation of fluid in the subarachnoid space causes a more or less extensive hernial bulging into the neighboring soft parts, which, when it attains sufficient dimensions, appears in the form of a sac. If the spinal cord takes no part in the tumor it is called a **meningocele.** Like the myelomeningocele, it is most commonly found in the sacral region, where defects of the spinal canal, in the form of holes and clefts in the vertebral arches, or even in the bodies of the vertebræ, occur most frequently. For example, it is not rare for the hiatus sacralis to extend up to the third sacral vertebra, owing to a broad cleft in the arch of the fourth sacral vertebra.

Usually the sac of a meningocele protrudes posteriorly (*meningocele posterior*), and may either be concealed in the soft parts (*spina bifida occulta*) or raise the skin above the surface; but instances also occur where the cysts press forward into the pelvis (*meningocele anterior*).

With a defect in the wall of the vertebral canal a hernial protrusion of the pia mater may also be produced by a dilatation of the central canal of the spinal cord, causing a larger or smaller portion of the spinal cord, together with its membranes, to assume the form of a cystic tumor, called a **myelocystocele**, a **hydromyelocele**, or also (in England) a *syringomyelocele.*

According to von Recklinghausen, the wall of these sacs is formed, in the main, of the spinal membranes, but is lined on the inner surface by a cylindrical epithelium, and has at some part of its inner surface an area medullo-vasculosa—usually on the ventral, seldom on the dorsal side. Corresponding with this condition, the nerve-roots, if they are present, spring mostly from the ventral, seldom from the dorsal wall of the sac. The cavity itself is crossed neither by bands nor by nerves.

Myelocystoceles occur, in the majority of cases, in conjunction with lateral clefts of the vertebral canal, and have a tendency, also, to be combined with *defects* and *asymmetries of the bodies of the vertebræ*, leading often to *shortening of the trunk;* sometimes affecting only the dorsal region, and sometimes including also the lumbar region. There is often, also, ecstrophy of the bladder, intestine, and abdominal cavity.

Myelocystoceles are mostly covered only by the outer skin, but are sometimes concealed deep down in the soft parts. They may furthermore be combined with meningoceles, producing **myelocystomeningoceles.**

Von Recklinghausen holds that, in the production of the various forms of hernial protrusion of the pia mater from the vertebral canal, the primary disturbances are always the local defect in the bony vertebral canal and the deficient development of the dura mater, which latter is often entirely wanting at the seat of protrusion. Taruffi believes that in some cases the cause of the spina bifida lies in a vascular hyperplasia of the primitive cord. The cysts push up from some distance below the surface, and, if they attain sufficient size, raise the skin. In rare cases their top may reach the surface. Smaller ones remain buried in muscle and fat beneath the fascia of the back (*spina bifida occulta, cryptomerorachischisis*). As to the origin of myelocystoceles and myelocystomeningoceles, one cannot, according to von Recklinghausen, ascribe as a cause either the persistence of the connection between the neural canal and the epiblast, or an interposition of fœtal membranes between the primitive cord and the epiblast, or an excessive stretching of the medullary groove-wall through bending of the axis of the embryo. According to him, the myelocystocele is a deficient growth in the long axis of the vertebral column, characterized anatomically by shortness of the column, by failing of vertebræ or portions of vertebræ, by separation of bony wedges from the bodies of the vertebræ, and by unilateral defects in the arches. The medullary tube then, pursuing its normal development, becomes too long for the vertebral canal, and consequently undergoes curling or kinking, and there is a tendency to a partial protrusion at the point where the bend is sharpest. Marchand, on the other hand, holds that this hypothesis does not fit all cases; and Arnold also believes that the causal relations between arrests of development in the muscle-plates and vertebral elements on the one hand, and those of the neural canal on the other hand, are not constant, but that a variety of disturbing influences may give rise to one or more of these anomalies.

Where the protrusion shall take place depends on where the wall of the spinal canal is yielding—i.e., where clefts exist. It can take place posteriorly, laterally, or anteriorly. Most frequently the protrusion lies posteriorly and at one side of the median line. At the summit of the sac one membrane, which may be looked upon as the dura, is always wanting. The growth of myelocystic and meningocystic sacs is to be attributed to congestive and inflammatory transudation. Occasionally marks of inflammatory change are found, consisting in thickenings of the pia and adherent membranes and threads in the interior of the sac.

In cases of rachischisis there is not infrequently, according to von Recklinghausen, a **division of the spinal cord into two parts** (*diastematomyelia*), usually where the rachischisis is total—that is, where generally only rudiments of spinal cord are indicated. Where there is partial rachischisis such rudiments are rarer; but the separate cords are more fully developed, and the fibrous and bony envelopes may at the beginning and end of the cleft send dividing septa between them. Cases occur where each cord-half shows an H-shaped area of gray matter. The duplications of the cord in spina bifida and rachischisis are to be regarded not as true double formations with duplication of the cord-substance; they represent only a divergence, a faulty union of the elementary symmetrical cord-halves.

In rare cases there is duplication of the central canal without external division of the cord (Wagner, Schüppel, Pick).

The human vertebral column is (Wiedersheim) an organ in process of retrogression, and the pelvic girdle is proportionately thrown into prominence. This is evidenced by the fact that embryos of 9–10 mm. in length have thirty-eight vertebræ, while in the adult man there are only thirty-three or thirty-four. When the embryo is six weeks old the thirty-sixth to the thirty-eighth vertebræ coalesce into a single mass, in which the thirty-fifth also joins later. According to Rosenberg, the first sacral vertebra unites with the sacrum later than the second, and the second later than the third. As development becomes higher, therefore, the pelvis becomes more prominent anteriorly and sacral vertebræ disappear. The number of the latter varies between four and five. A decrease in the number of lumbar and dorsal vertebræ is not rare, and coalescence between them, as also partial defects of vertebræ, occur. (On increase of the number of vertebræ and formation of a tail, see § 153.)

§ 145. The cleft-formations and hernial sac-formations which have been described in § 144 all occur in corresponding forms, also, in the cephalic portion of the neural canal, and lead to a series of malformations, some of which persist in post-embryonic life.

In the most exaggerated forms the bony portions and the skin of the cranial vault are wanting (Figs. 281 and 285), and the surface of the base of the skull is covered only by a tegumentary layer of vascular, spongy tissue, usually containing scattered hæmorrhages, and beneath which there may be rudiments of brain-substance. Modifying the term used in rachischisis to suit the condition as found here, we may call this tissue the *area cerebro-vasculosa*.

Fig. 285.

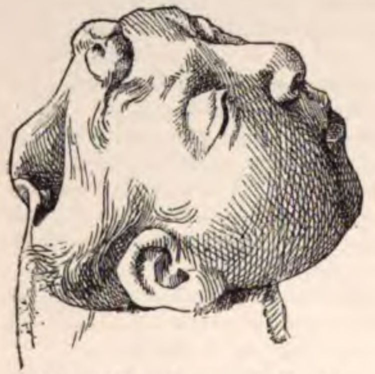

Fig. 286.

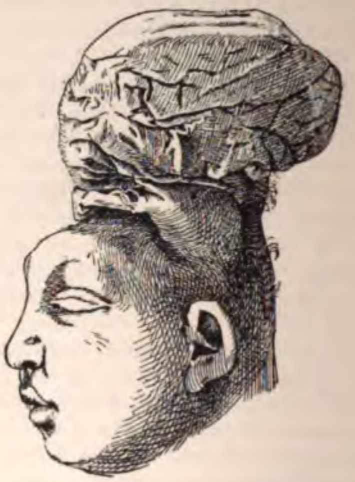

FIG. 285.—Anencephalia et acrania. (Reduced one half.)

FIG. 286.—Cranioschisis with encephalomeningocele.

The cleft-formation may be confined to the cranial vault, but frequently it includes vertebral arches as well (Fig. 281), and extends to a greater or less distance down the back.

The deficiency in the cranial vault is called **acrania** and **cranioschisis**, and when combined with a vertebral cleft it is called **craniorachischisis.**

In this latter condition the vertebral column is usually stunted and bent so that the head is drawn sharply backward and the face turned upward (Fig. 281). In these malformations the stunted development of the forehead, and the great prominence of the eye resulting therefrom, give the appearance of a frog's head (*frog fœtus*).

The abnormalities in the individual bones of the cranium are by no means always the same; and between cases where the cranial vault and walls are entirely wanting and cases of **microcephalus**, where the vault is properly closed, but the cranium abnormally small, there are the most various intermediate gradations (Figs. 285 and 287). Similarly the brain-substance present varies in amount and in the extent to which it has reached development into recognizable portions of brain. If there is no microscopically recognizable portion of brain-substance present the case is called one of **total anencephalia**; where the deficiency is only partial it is called **partial anencephalia.** If the rudiment of brain is small, and confined to the posterior portions which are inclosed in the cervical vertebræ, it is also called **derencephalia.**

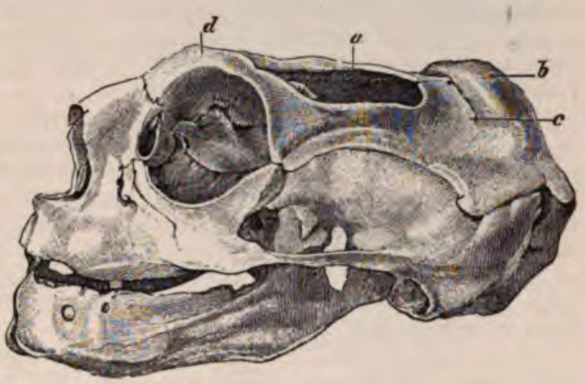

FIG. 287.—Partial agenesia of the bones of the cranium in anencephalia. *a*, Defect; *b*, Occipital portion of skull; *c*, Parietal bone; *d*, Frontal bone. (Reduced one fifth.)

The tegument covering the base of the skull is often only a mass of spongy tissue of slight or moderate thickness. But sometimes sacs (Fig. 275, *a*, and Fig. 285) protrude from the opening between the rudimentary parietal and the occiput or the frontal bone (Fig. 287, *a*, *b*, *c*, *d*), consisting of a vascular connective tissue containing cystic cavities and occasionally also rudiments of brain-substance. Sacs which contain only meninges with cysts are called *meningoceles;* those containing also brain-substance are called *encephalomeningoceles* (cf. § 146).

Geoffroy-St. Hilaire, Förster, and Panum regard acrania and anencephalia as due to an abnormal accumulation of fluid in the cerebral vesicles—a *hydrocephalus*—occurring before the fourth fœtal month. Dareste and Perls oppose this view, drawing attention to the circumstance that in acrania the base of the skull is mostly arched inward and not pressed outward, and seek for the cause of this condition in a pressure acting on the skull from without (Perls) and exerted by the cephalic cap of the amnion, lying snugly against the cephalic bend and hindering the development of the cranium. Lebedeff looks for the cause of acrania in an abnormally sharp curvature of the body of the embryo, occurring where the cephalic end of the embryo has elongated abnormally, or the cephalic envelope has lagged behind in development.

Through the sharp curvature the change of the medullary plate into the neural canal is supposed to be prevented, or the already formed canal to be destroyed again. This would explain the absence, later, of the brain, together with its membranous and bony coverings. Lebedeff supposes the cystic formations which are found lying on the base of the skull to result from folds of the medullary plate which become sunk in the mesoderm and then snared off.

It is very likely that acrania is not always due to a single cause; and while in one case the influences brought forward by Perls and Lebedeff, or adhesions to the membranes (Fig. 275), may have checked the development of cranium and brain, yet in other instances the malformation must probably be ascribed to a primary agenesia already determined in the germ.

§ 146. Where the cranium is in general properly closed, but presents **partial deficiencies,** portions of the cranial contents may protrude in the form of a hernial sac, and it is hence spoken of as a **hernia cerebri** or **cephalocele** (Fig. 288). Defects of ossification (Ackermann), or deficient resistance of the membranous cranial envelope, are doubtless usually the primary cause; but adhesions of the meninges with the amnion (St. Hilaire) may also be a cause.

The size of the protruding sac varies greatly. It may be so small as to be found only by careful examination, or it may be so large as to approach the brain in volume. Where accumulation of fluid in the subarachnoid space has caused only the arachnoid and pia to protrude, the tumor is a **meningocele**; where brain-substance also protrudes, it is a **meningo-encephalocele.** A protrusion of brain-substance and pia without accumulation of fluid is called an **encephalocele**; if the protruding brain-substance contains part of a ventricle filled with fluid it is called a **hydrencephalocele.**

These brain-hernias appear mostly in the occipital region (*hernia occipitalis*) close above the foramen magnum (Fig. 288), at the root of the nose, and at the lower end of the frontal suture (*hernia syncipitalis*); but they occur also in the region of the temple, at the base of the skull, in the orbital fissure, and elsewhere.

Marked stunting in the development of the anterior of the three cerebral vesicles may leave the cerebrum single (St. Hilaire's *cyclencephalia* or *cyclocephalia*), while at the same time a deficient separation of the ocular vesicles takes place. Where the stunting is very marked, only a single eye may be formed in the middle of the forehead, or there may be two united together and lying in a single orbit (Fig. 289); and this malformation is called **cyclopia** or **synophthalmia**, and **arrhinencephalia** (Kundrat). The nose is also stunted, and present only as a cutaneous tag attached above the eye and devoid of bony foundation (*ethmocephalia*).

Fig. 288.

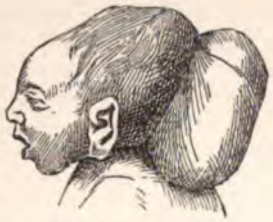

FIG. 288.—Hydrencephalocele occipitalis.

Fig. 289.

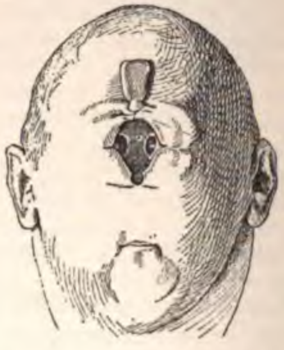

FIG. 289. — Synophthalmia or cyclopia.

Where the eyes are separate, yet abnormally close together, the nose in general may be normal, but at the root it is very small (*cebocephalia*).

In the severer forms of the malformation the ethmoid and the nasal septum may be wanting, and the upper lip and palate cleft in the median line, or laterally on one or on both sides (Kundrat). In the milder forms the forehead is merely reduced in size and pointed like a wedge.

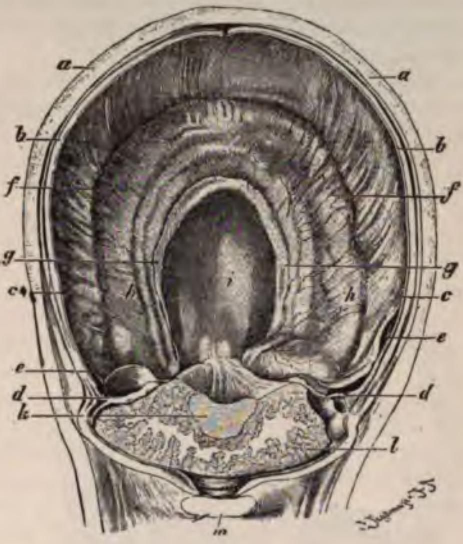

FIG. 290.—Cranial cavity of a synophthalmus microstomus opened by a frontal section (viewed from behind). *a*, Skin and subcutaneous tissue; *b*, Cranial vault; *c*, Dura mater; *d*, Tentorium; *e*, Arachnoid; *f*, Posterior surface of the cerebrum, consisting merely of a thin-walled sac covered with pia mater; *g*, Tumified border of the cerebral sac; *h*, Subarachnoid space behind the cerebral sac; *i*, Cavity of the cerebral sac, communicating with the subarachnoid space by the enlarged transverse fissure; *k*, Section through the corpora quadrigemina; *l*, Section through the cerebellum; *m*, The atlas. (Four-fifths natural size.)

In the severest grades of these malformations the cerebrum consists of a sac (Fig. 290, *i*) occupying more or less of the cranial cavity and filled with a clear fluid; where the sac does not lie against the cranial wall the intervening space is taken up by fluid distending the subarachnoid space (*h*). In milder instances only individual portions of the brain are wanting in development, those mostly affected being the olfactory nerve and olfactory bulb, the corpus callosum, a part of the convolutions, etc. The optic thalami are often blended together. The chiasma and optic tracts may be either wanting or present. The corpora quadrigemina (*k*), the pons, the medulla oblongata, and the cerebellum (*l*) are usually unaffected.

(c) *Malformations of the Face and Neck.*

§ 147. The development of the **face** is subject not infrequently to disturbances leading to more or less marked malformations, which may appear alone or be combined with malformations of the cranial portion of the head. Where the frontal process and the maxillary processes of the first branchial arch remain in an entirely rudimentary state, or are more or less completely destroyed by pathological processes, there is present at the site where the face should be merely a surface or cleft (**aprosopia** and **schistoprosopia**), which may or may not be combined with malformations of the nose and eyes.

But more frequent than these large defects are smaller clefts involving the lip, the alveolar process of the upper jaw, the upper jaw itself, and the hard and soft palates (**cheilo-gnatho-palatoschisis**). This malformation establishes a communication between the mouth and the nasal cavity (Fig. 291). The hard palate, where it abuts against the vomer, is cleft in the median line where it meets the soft palate. In the alveolar process of the upper jaw the cleft runs between the eye-tooth and the lateral incisor, or between the lateral and central incisors. The malformation may be bilateral (Fig. 291) or unilateral, primary and hereditary or secondarily acquired, one of the causes of the latter condition being amniotic adhesions (Fig. 276).

Frequently the cleft involves only special portions of the region above mentioned, as the upper lip (*harelip, labium leporinum*), or, what is rarer, only the hard or only the soft palate. The mildest degree is indicated by a *notch* or a *cicatricial line in the lip*, or by a *bifurcation of the uvula*.

Fig. 291.

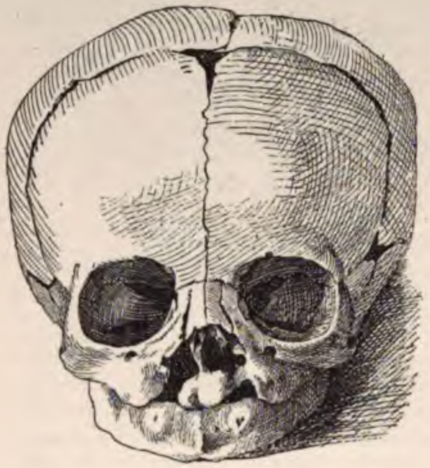

Fig. 292.

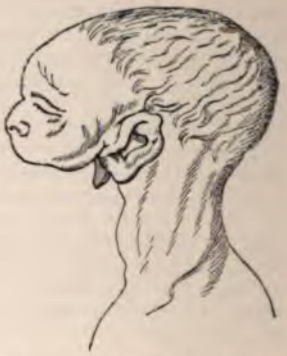

FIG. 291.—Double cheilo-gnatho-palatoschisis.

FIG. 292.—Agnathia and synotia (Guardan).

Prosoposchisis (Fig. 276, *e*) is the term applied to a cleft running obliquely from the mouth to an orbit. It is usually associated with malformations of the brain. Morian distinguishes three varieties. The first commences on the upper lip as a harelip, passes into the nostril, thence around the ala nasi toward the orbit, and may extend even beyond the orbit. The second variety begins likewise in the region of a harelip, but extends outward from the nose toward the orbit. The third variety extends from the corner of the mouth outward through the cheek toward the canthus of the eye, and divides the superior maxillary process externally to the canine tooth. A *transverse cleft of the cheek* also occurs, coursing from the corner of the mouth toward the temporal region.

Median facial clefts also occur, and may involve the nose and upper jaw, and also the lower jaw, or even extend as far down as the sternum. With this malformation the tongue may also be cleft (Wölfler).

All of the above-described clefts may be confined to small portions of the regions mentioned, and may also attain various depths.

Where the inferior maxillary process of the first branchial arch is tardy in its development, the inferior maxilla becomes also imperfectly developed, and may be entirely wanting, producing the malformations known as **brachygnathia** and **agnathia** (Fig. 292), and the appearance presented is as if the lower half of the face had been cut away; the ears are sometimes so close to each other as to touch (*synotia*). Usually the superior maxillary processes are also imperfectly developed, and frequently the ear is misshapen.

Malformations of the mouth, as abnormally large size (*macrostomia*), abnormally small size (*microstomia*), closure (*atresia oris*), and duplication (*distomia*), are all rare.

Where the embryonic external branchial clefts or internal branchial pockets fail in part to close, fistulæ opening either externally or internally, or closed cysts, remain. The former condition is called **fistula colli congenita.** The mouths of the external fistulæ are generally found at the side of the neck, more rarely approaching, or actually in, the median line; those of the internal fistulæ open into the pharynx, trachea, or larynx. Frequently slight remains of the branchial pockets form merely diverticula of the latter organs. The fistulæ are mostly clothed with a mucous epithelium, sometimes ciliated, originating, therefore, from the visceral branchial pockets—according to von Kostanecki and von Mielecki, mostly from the second. In rare cases a complete branchial fistula is found, having both an external and an internal opening.

The **branchial cysts** which arise from the branchial pockets are sometimes clothed with mucous membrane (ciliated epithelium), are filled with fluid, and receive the name of *hydrocele colli congenita*; sometimes they are lined with an epidermal covering, contain masses of epidermal cells, and are therefore reckoned among the *atheromata* and *dermoid cysts.* Arrests in development of the anterior end of the branchial arch (mesobranchial field) and in the region of the third branchial pocket (the site of origin of the thymus) and branchial cleft may lead to the formation of *dermoids in the submental region, at the root of the tongue, and in the mediastinum.*

The face and neck are developed in part from a single embryonic rudiment, in part from paired rudiments. The latter are represented in the branchial or visceral arches growing from the lateral portions of the base of the skull ventrally in the primitive throat-wall. The single rudiment, called the frontal process, is a prolongation downward of the base and vault of the skull, and is, in fact, the anterior end of the skull. Between the individual branchial arches there are at a certain period cleft-like depressions or branchial pockets.

The frontal process and the first branchial arch form the borders of the great primitive mouth, which has a diamond shape. In the course of development the first branchial arch sends out two processes, of which the shorter applies itself to the under surface of the forehead and forms the upper jaw, while from the lower and longer one the lower jaw develops. The frontal process, which forms the anterior border of the mouth, produces a wide and long forehead and then pushes on two lateral processes, called lateral nasal processes. By further differentiation of the central portion of the frontal process the septum narium is formed, which, by means of two spurs called the inner nasal processes, produces the borders of the nostril and the nasal furrow. The lateral nasal processes are the lateral portions of the skull, and develop within themselves later the ethmoid labyrinth, the cartilaginous roof, and the sides of the anterior portion of the nares. At a certain stage they form with the superior maxillary process a fissure running from the nasal furrow to the eye, and called the lachrymal fissure.

The mouth is at first simply a great cavern, but is soon subdivided into a lower and larger digestive and an upper and smaller respiratory portion. This is done by the development, from the superior maxillary processes of the first branchial arch, of the plates which are to form the palate, and which begin in the eighth week to unite with one another and also with the lower edge of the nasal septum. The union of these lateral plates to form the palate begins anteriorly and progresses backward.

The union of the contiguous surfaces of the frontal and nasal processes with the superior maxillary processes forms the cheek and a continuous superior maxillary border, from which are developed later the lip and the alveolar process of the upper jaw-bone and the intermaxillary bones, while the nose develops from the frontal process. The intermaxillary bones are formed as two entirely distinct symmetrical bones, but unite early one with the other, and both with the upper jaw-bones.

(d) *Faulty Closure of the Abdominal and Thoracic Cavities, and the Accompanying Malformations.*

§ 148. The construction of the body-form from the flat embryonic layers begins by a turning over and drawing together of the layers at the periphery of the embryonic area, so that they become transformed into two tubes, one of which is the abdominal wall, the other the alimentary canal (Hertwig).

The infolding of these layers takes place at the cephalic and caudal ends as well as at the sides; and as these folds approach one another from all directions, those which are to form the abdominal wall produce a tube whose interior finally communicates only at the parietal umbilicus, by means of a tubular prolongation, with the cavity of the extra-embryonic portion of the blastodermic membrane. While these lateral and ventral walls of the embryo are being thus formed, within the body the intestinal furrow closes to form a tube which is in communication at only one point—namely, at the visceral umbilicus (within the above-mentioned communication of the abdominal cavity)—with the cavity of the umbilical vesicle, the channel between the two being called the omphalomesenteric duct.

The omphalomesenteric duct becomes obliterated in the sixth week. The complete closure of the abdominal cavity follows in the eighth week.

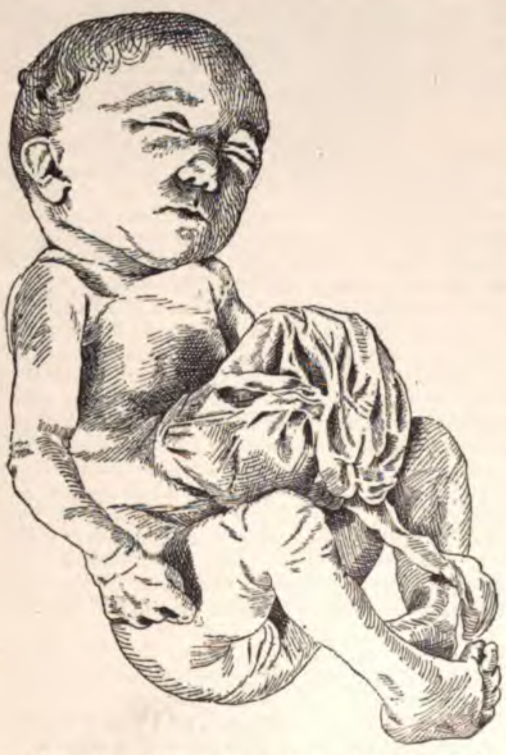

FIG. 293.—Hernia funiculi umbilicalis. (Two-thirds normal size.)

Arrests of development in the formation of the abdominal wall may take place at various points and be more or less marked. They are most frequent in the region of the umbilicus, where the closure is latest. Where faulty development of the abdominal wall at this point—leaving the abdominal cavity closed over a greater or less area only by peritoneum and the covering of the umbilical cord (the amnion)—gives rise to hernial protrusion over this area (Fig. 293), the condition is called **omphalocele, hernia funiculi umbilicalis,** or **umbilical hernia.** The remnant of the cord is situated either on the summit of the protrusion or at one side, and is more or less shortened.

The anterior abdominal walls may entirely or almost fail to unite—conditions called **fissura abdominalis, gastroschisis completa,** and **thoracogastroschisis,** and characterized by the undeveloped abdominal coverings not having been separated from the amnion, but running into it. The greater bulk of the abdominal contents then lie in a sac composed of peritoneum and amnion; or the peritoneum may be wanting also. The umbilical cord is also often wanting, and the umbilical vessels run to the placenta without joining one another.

Failure of the chest-wall to close is called **thoracoschisis.** The heart, covered with the pericardium or entirely free, may push out through an opening in the cardiac region. This condition is called **ectopia cordis.**

Where the failure to close is confined to the sternal region it is called **fissura sterni.** This may involve the whole sternum or only a part of it; it may affect only the bones, or it may affect the skin also.

Where the urinary bladder prolapses through a cleft in the abdominal wall, the condition is known as **ectopia vesicæ urinariæ.**

Clefts of the abdominal wall, whether total or partial, are not infrequently complicated by clefts of the parts lying behind the abdominal wall. Where a cleft of the lower abdominal wall is combined with a cleft of the bladder also, so that the posterior wall of the bladder protrudes through the abdominal opening, the condition is called **fissura** or **ecstrophia** or **inversio vesicæ urinariæ** (Fig. 294, *c*). Sometimes the pelvic girdle and the urethra are also cleft, converting the latter into an exposed trough (Fig. 294, *e*). The ecstrophy is then said to be complicated with **fissura genitalis** and **epispadias.**

Where an abdominal fissure, or an abdominal fissure together with ecstrophy of the bladder, is complicated with fissure of the intestine, the condition is called **fissura abdominalis intestinalis** or **vesico-intestinalis.** The intestinal fissure is situated in the cæcum or in the beginning of the colon, and the mucous membrane of the intestine protrudes in the same manner as the posterior wall of the bladder; and hence it is called **ecstrophia** or **inversio intestini.**

If the omphalomesenteric duct does not undergo its normal atrophy, an appendix of intestine, called **Meckel's diverticulum,** remains. This diverticulum proceeds from the outer surface of the gut, having generally the appearance of a glove-finger, and either ends blindly or is attached at the umbilicus, sometimes being dilated at the ends. It may be adherent in the umbilical ring and its mucous surface may protrude (*ectopia intestini, adenoma umbilicale*). In very rare cases a cyst lined with mucous membrane is found in the abdominal wall (a remnant of the omphalomesenteric duct).

Umbilical hernia and clefts in the upper part of the abdominal wall are often combined with craniorachischisis, while ecstrophy of the bladder and intestine is often combined with myelocystocele; and von Recklinghausen regards the two malformations as bearing some relation to each other. Large abdominal clefts are furthermore often associated with lordotic or scoliotic curvatures of the spinal column.

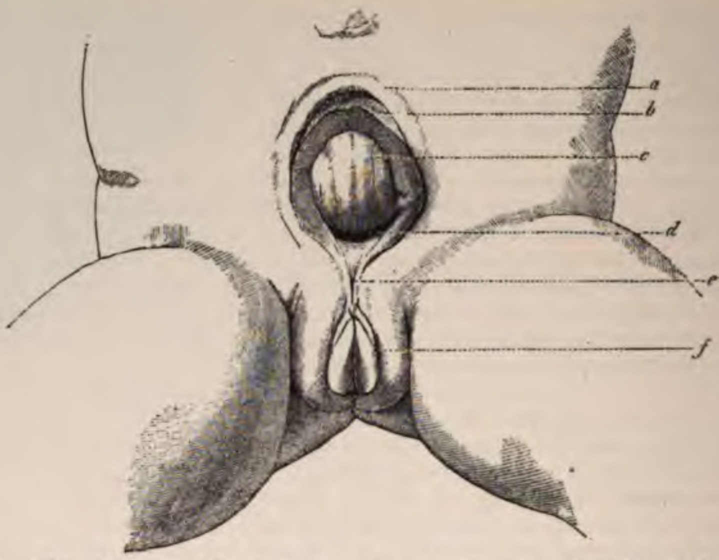

FIG. 294.—Fissura abdominis et vesicæ urinariæ, in a girl eighteen days old. *a*, Border of the skin; *b*, Peritoneum; *c*, Bladder; *d*, Small bladder-cavity composed of the trigone; *e*, Trough-like urethra; *f*, The labia minora.

(*e*) *Malformations of the External Genitalia and of Parts belonging to the Anal Region, caused by Arrested Development.*

§ 149. Malformations of the external genital organs may be associated with malformations of the abdominal wall, the bladder, and the internal genital organs, or they may occur without these associations. **Total absence of the external genitalia** may be the only defect, but it usually forms only a part of a more extensive malformation of the parts of that

Fig. 295.

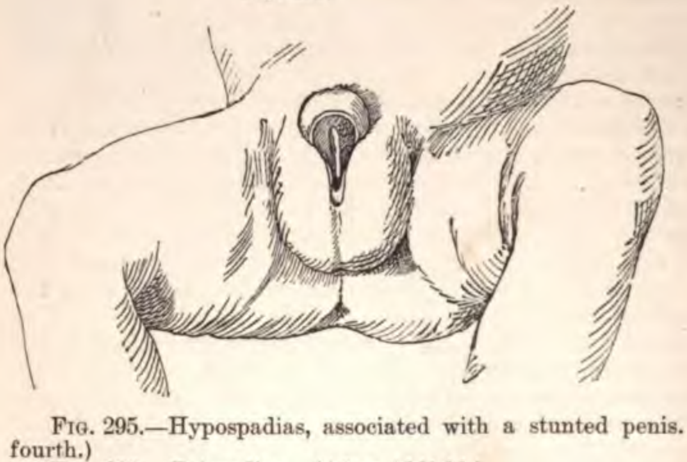

Fig. 296.

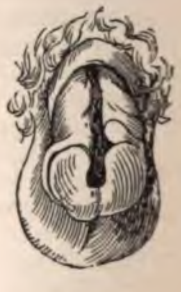

FIG. 295.—Hypospadias, associated with a stunted penis. (Reduced one fourth.)

FIG. 296.—Epispadias. (After Ahlfeld.)

region, and, as a rule, is associated with defects in the internal genital organs (Fig. 297).

A rare condition is a **duplication of the penis** or of the penile urethra, one canal giving passage to the urine, while the other communicates with the sexual organs. A **dwarfed condition of the penis**, resembling the clitoris, is more common. It is usually associated with **hypospadias**, the urethral opening being beneath the glans, the body or the root of the penis (Fig. 295), or, in extreme cases, behind the scrotum (*hypospadias perineoscrotalis*). The same degrees of hypospadias may exist in penises otherwise normal, being due simply to a more or less complete covering of the sexual furrow from which the urethra normally develops.

Epispadias (Fig. 296) is the term applied to the condition in which the urethra opens upon the dorsal aspect of the penis. It is less common than hypospadias, and results from an incomplete or retarded closing of the pelvic cavity. of such a character that the cloaca is divided into an anal and a genital portion (Thiersch). Sometimes the two penile halves may remain separate, with or without ecstrophy of the bladder or an incomplete closure of the abdominal cavity.

The **prepuce** is subject to the following anomalies: it may rarely be **entirely absent**, or, more frequently, **abnormally short**; often it is **hypertrophied**, and this hypertrophy may be associated with a stenosis of the orifice, so that it cannot be retracted (**hypertrophic phimosis**).

Deficient development of the scrotum is usually associated with retention of the testis in the abdominal cavity or in the inguinal canal, and causes the external genitals to look like those of the female—a result which is heightened when the penis is small or ill developed.

In the female the **clitoris and the labia majora and minora may be deficiently developed**; **epispadias and hypospadias** may also occur, the former associated with ecstrophy and, perhaps, incomplete closure of the abdomen (Fig. 294). In hypospadias the urethra opens into the vagina.

The **urethra may be absent** in either sex (Fig. 297). In young females the bladder may open directly into the vagina.

Urethral atresia can also occur in either sex, and results from a local defective development or an obliteration of the orifice. An accumulation of urine may, in these cases, cause extreme dilatation of the bladder (Fig. 297).

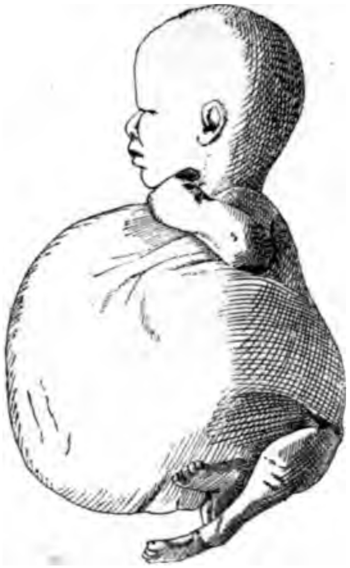

FIG. 297.—Complete absence of the urethra and external genitals, with extreme distention of the abdomen by an accumulation of urine in the bladder; and compression and dwarfing of the lower extremities. (In the posterior wall of the bladder there were rudiments of tubes and ovaries.)

An **abnormal narrowness of the urethra** may exist in a portion of its course or throughout its whole extent. Its lumen may be compromised by a hypertrophy of the colliculus seminalis.

Occasionally the urethra opens by *multiple orifices*, and sometimes there is a blind canal in the glans penis, lying beside the normal urethra.

An **allantoic cloaca,** due to arrested development, may persist at birth and form a common outlet for the bladder and intestine. Frequently the bladder is divided, the rectum not existing, and then the ileum opens directly into the cloaca. In less anomalous cases there is merely a failure in the separation of the intestinal outlet from the urogenital sinus—i.e., from the genital and urinary orifices. Since the external depression which forms the anus is wanting in these cases, they are designated as **atresia ani,** and, according to the association of the intestine with the neighboring structures, they are classed as *atresia ani vesicalis, urethralis,* or *vaginalis.*

When the rectum communicates neither with the urogenital sinus nor with the cutaneous anal depression, the condition is called *atresia simplex.* In such cases the rectum is often imperfectly developed.

(*f*) *Malformations of the Extremities due to Arrest of Development.*

§ 150. The extremities appear first as thickenings of the cutaneous plates of the embryo, which after elongation become divided off into the component divisions of the extremities by shallow furrows.

Defective development of the extremities is not rare, and may owe its origin to a deficiency in the primary differentiation of the embryo, be secondary to some disturbance in the development of the limb or the bones, or result from constrictions caused by strands of the membranes or loops of the umbilical cord. The cause of such defective development of the extremities may sometimes be referred to precedent malformations of the central nervous system.

They are grouped into the following classes, according to the degree of malformation:

1. *Amelus.* The extremities are either all entirely wanting or are represented by mere stumps or wart-like rudiments (Fig. 298).
2. *Peromelus.* All the extremities are dwarfed.
3. *Phocomelus.* The hands and feet are developed, but are attached directly to the shoulder and pelvis respectively.
4. *Micromelus* (microbrachius, micropus). The extremities are fully differentiated, but remain abnormally small (Fig. 299).
5. *Abrachius* and *apus.* Absence of the upper extremities with well-developed lower extremities, or vice versa.
6. *Perobrachius* and *peropus.* The arms and thighs well developed; the forearms, hands, legs, and feet malformed.
7. *Monobrachius* and *monopus.* Absence of a single upper or lower extremity.
8. *Sympus, sirenomelia, symmyelia.* The lower extremities are coalescent in a position of semi-rotation around their axes, so that their external aspects are in contact (Figs. 300 and 301). The pelvis is usually absent, as are also the external genitals, bladder, urethra, and anus. The feet may be entirely wanting (*sympus apus*) and only a few toes be present (Fig. 300), or in other cases (Fig. 301) a single foot (*sympus monopus*) or both feet (*sympus dipus*) may be present.
9. Of the single bones, the radius, fibula, patella, clavicle, and scapula are those most frequently absent.
10. *Achirus* and *perochirus.* The absence or dwarfing of the whole

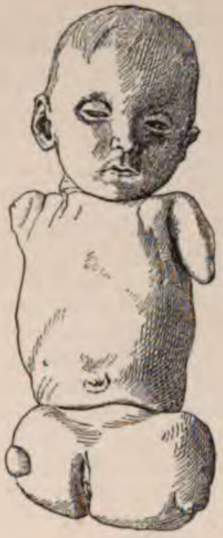

FIG. 298.—Amelus.

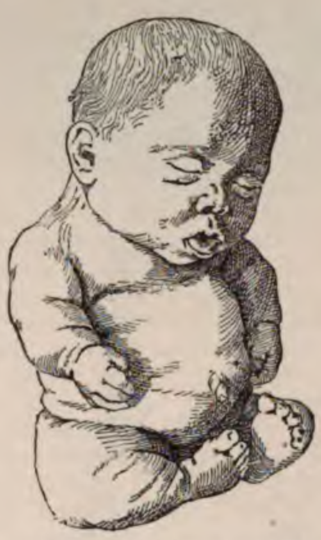

FIG. 299.—Micromelus with cretinitic facies.

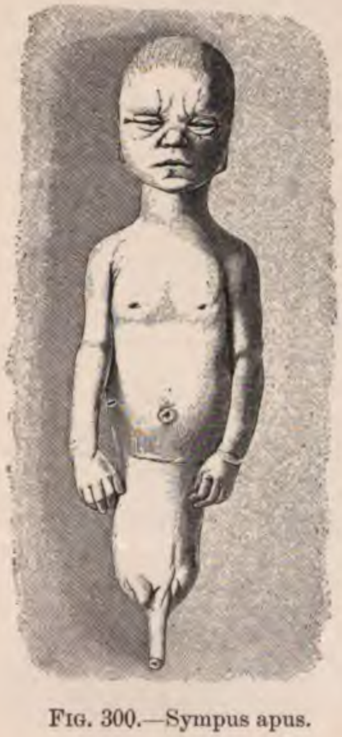

FIG. 300.—Sympus apus.

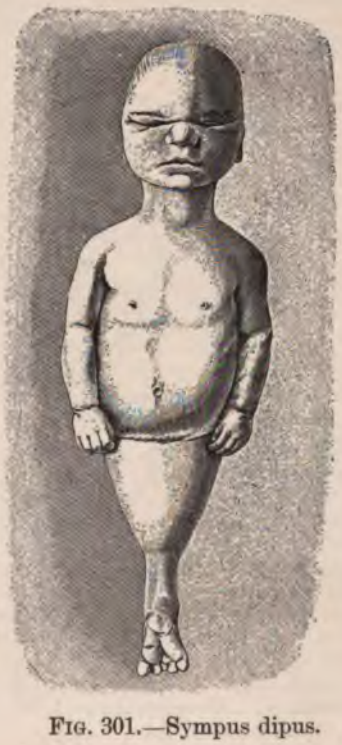

FIG. 301.—Sympus dipus.

hands and feet is rare. More frequently individual fingers or toes are wanting or stunted (*perodactylus*), or coalesce with others (*syndactylus*) (Fig. 302, Fig. 303, *c*, Figs. 304 and 305. Cf. also § 139, Figs. 277 and 278, page 389).

Fig. 302.

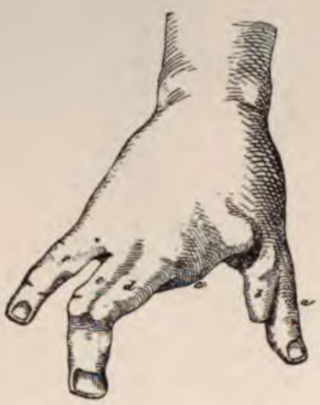

Fig. 303.

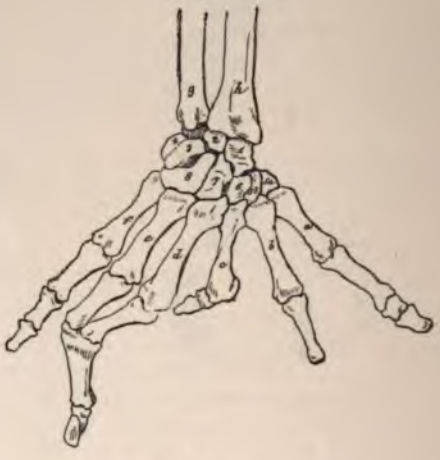

Fig. 304.

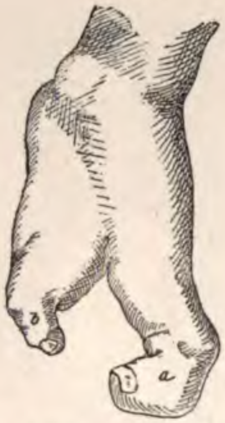

Fig. 305.

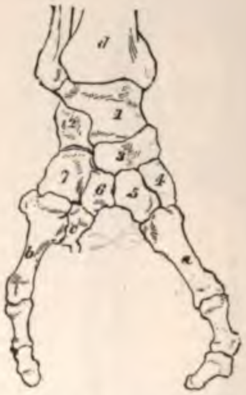

FIG. 302.—Malformation of the right hand (perochirus) with coalescence of the fingers. (After Otto.) *a*, Supernumerary thumb; *b*, Thumb proper; *c*, Dwarfed index-finger; *d*, Middle finger; *e*, Ring-finger; *f*, Little finger.

FIG. 303.—Bones of the perochirus depicted in Fig. 302, shown in their dorsal aspect. (After Otto.) *a*-*f*, Same as in Fig. 302; *g*, Ulna; *h*, Radius; 1, Os naviculare; 2, Os lunatum; 3, Os triangulare; 4, Os pisiforme; 5^a, Os multangulum majus superfluum; 5^b, Os multangulum ordinarium; 6, Os multangulum minus; 7, Os capitatum; 8, Os hamatum.

FIG. 304.—Peropus dexter. (After Otto.) *a*, Great toe; *b*, Little toe.

FIG. 305.—Bones of the foot depicted in Fig. 304, in the dorsal aspect. *a*, Big toe; *b*, Little toe; *c*, Rudiment of the third toe; *d*, Tibia; *e*, Fibula; 1, Talus; 2, Calcaneus; 3, Os naviculare; 4, Os cuneiforme majus; 5, Os cuneiforme minus; 6, Os cuneiforme tertium; 7, Os cubiforme.

2. *Abnormal Positions of the Internal Organs and of the Extremities.*

§ 151. Of the abnormal positions of the internal organs, the most important is the **situs inversus viscerum**—i.e., a *lateral transposition of the thoracic and abdominal viscera.* It has been observed in double monsters as well as in single individuals, and may be restricted to a simple malposition of the heart alone, or, more rarely, of only the abdominal organs. Other malpositions affect most frequently the abdominal viscera. The kidney, for example, is not rarely malplaced (*dystopia renis*), in which cases it is usually found below its normal site, near or even in front of the sacral promontory. The testis is sometimes retained within the abdominal cavity (*ectopia interna seu abdominalis testis; cryptorchismus*), or in the inguinal canal (*ectopia inguinalis*), or at the external ring (*ectopia pubica*), or, finally, at some point between the latter situation and its normal position (*ectopia cruroscrotalis, perinealis*, or *cruralis*). *Abnormal positions of the intestine*, especially of the large intestine, are not rare.

Among the abnormal positions of the extremities **congenital luxations** are of particular interest. They are most common at the hip, more rare at the elbow, shoulder, and knee. Von Ammon, Döllinger, Grawitz, and Krönlein regard them as the result of arrested development. At the hip the acetabular socket remains small and imperfect, and the head of the femur is more or less incompletely developed, so that it is readily displaced, usually backward (luxatio iliaca). At birth the ligamentum teres is always intact, but stretches when the limb is used, and may be ruptured. The capsule is at first intact, but the continued pressure between the bony surfaces may cause it to become perforated, in which case a new joint may be formed by the proliferation of the surrounding tissues.

Abnormal positions of the feet and hands are to be attributed sometimes to disturbances of development, sometimes to mechanical causes. The most important is **congenital club-foot** (**pes equinovarus**), which, according to Eschricht, is due to arrest of development leaving the foot in its fœtal position, with malformation of the bones and their articular surfaces. He describes the feet as lying at first with their dorsal surfaces against the abdominal wall of the fœtus. This position gradually passes into the normal through a revolution around the axis; but even at birth this rotation is not completed, the toes being still turned inward, and this persists until the act of walking gradually completes the change. In club-foot this fœtal position is exaggerated, the inner edge of the foot is abnormally raised, and the whole foot is in a position of plantar flexion. The shapes of the bones and joint surfaces are also abnormal, the collum tali being especially elongated (Hüter, Adams). If the children learn to walk, they tread upon the outer edges of the feet, which are flattened by the pressure, while the whole foot is more strongly inverted.

The congenital club-foot, though, as stated, usually the result of arrest of development, may occasionally be caused by an abnormal pressure due to a relatively small uterus (Volkmann). Under these conditions the positions known as **pes calcaneus** and **pes valgus** may be produced. They are characterized in part by a strong dorsal flexion, in part by a twisting, of the foot. Frequently the evidences of the pressure to which the feet have been subjected are seen in an atrophic condition of the skin and the relative positions of the bones.

The position of the hand designated as **clubbed hand** or **talipomanus** is caused by a rudimentary development of the radius, and is usually associated with other malpositions in the individual.

3. *Malpositions the Result of Excessive Growth or Multiplication of Organs or Parts of the Body.*

§ 152. A malformation known as **general giant growth** is the result of an excessive growth of the whole body, which may take place *in utero* or in after-life. New-born children weighing more than twenty-two pounds are on record. During extra-uterine life growth far beyond the usual maximum may take place.

Partial giant growth (cf. § 79) may also take place *in utero* or after birth, and usually affects portions of the extremities or the head. During extra-uterine life trauma sometimes gives an impulse to a pathological excess of growth.

In these hypertrophies of an extremity—as, for example, a finger—the structure of the part may preserve its general normal relations, all its constituents participating in the abnormal development. In other cases certain tissues monopolize the growth, as, for example, the soft parts, especially the fat. Furthermore, the enlarged soft parts may show a pathological structure, as exemplified by cases in which the blood- or lymph-vessels are abnormally developed. When the extremities are the seat of this growth the condition is usually designated as **elephantiasis.** When the thickened portions are sharply circumscribed they are usually regarded as **tumors**, and, according to their structures, are classed with the angiomata, lymphangiomata, or fibromata. On the trunk the hypertrophies usually resemble elephantiasis, but sometimes they assume the form of a neoplasm. The same is true where the parts affected belong to the face; the lips, cheeks, and tongue being not infrequently enlarged and distorted by a hyperplasia of the connective tissue richly endowed with lymphatic vessels.

Circumscribed hypertrophies of the bones occur in various parts of the skeleton, and are sometimes multiple. The bones of the head—those of the skull as well as those of the face—may be the seat of hypertrophy, which may be so extensive as to cause a deformity of one or both of these regions, a condition known as *leontiasis ossea* (Fig. 96, p. 219). Circumscribed hypertrophies also lead to the formation of *osteomata* or *exostoses*, often multiple. The bones of the hip and of the extremities may present hypertrophies which may involve single bones only, or may result in the formation of atypical, frequently multiple, masses of bone.

§ 153. **Supernumerary organs**, or a **multiplication of the parts of the skeleton and of the muscular system**, are not uncommon, and are the result either of changes occurring early in the development of the parts, or of the persistence of parts that are normally suppressed as development advances, in which latter case they may, perhaps, be regarded as examples of atavism.

1. **Duplications at the extremities.**

A duplication of a whole extremity, without involving either the shoulder or the pelvis, has never been observed in man. Duplication of the hands and feet is rare, but a number of cases are on record (Fig. 306). The number of fingers may reach nine or ten.

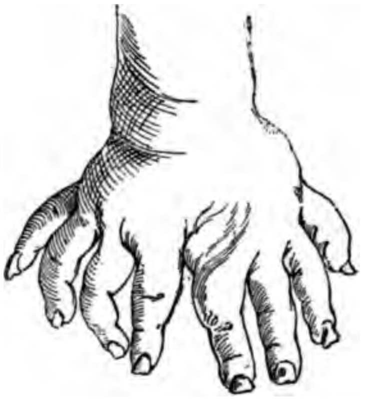

FIG. 306.—Polydactylism with duplication of the hand. (After Lancereaux.)

Supernumerary fingers (polydactylism) on a simple hand, where the extra fingers are attached at the radial or ulnar side of the hand, or intercalated between the normal fingers, are more common than a duplication of the whole hand (Fig. 307). Similar anomalies occur on the lower extremities (Fig. 308). Frequently the duplication involves only the first, or the first two, terminal joints of the fingers (Fig. 307). When attached to the edge of the hand the fingers may be well developed, or they may be mere rudiments. Occasionally they appear as small pedunculated fibrous tumors. In the fully developed supernumerary fingers the phalanges may articulate with the metacarpal or metatarsal bones of neighboring fingers, or with supernumerary bones of the hand or foot, which in turn may articulate with supernumerary carpal or tarsal bones.

Fig. 307.

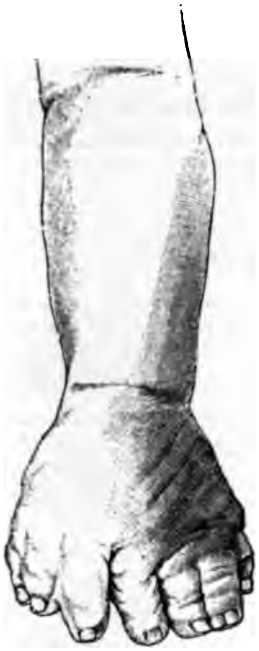

Fig. 308.

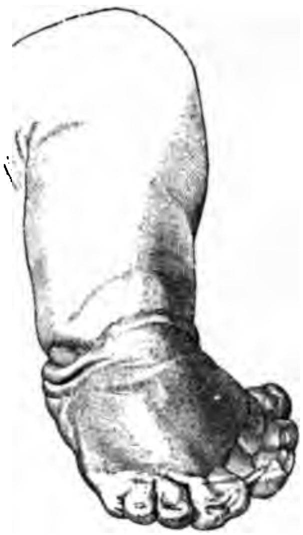

FIG. 307.—Polydactylism and syndactylism of the left hand. (Reduced one fifth.)

FIG. 308.—Polydactylism and syndactylism of the right foot. (Reduced one fifth.)

Polydactylism is sometimes inherited, sometimes the result of intrauterine influences and therefore independent of heredity.

2. **Supernumerary nipples and breasts** (**hyperthelia, hypermastia**) are not uncommon anomalies in both sexes, and are probably to be regarded as examples of atavism. They are usually situated on the thorax, along two lines running from the axillæ to the inguinal regions; but they may, rarely, be in other places—e.g., the axilla, shoulder, abdomen, back, or thigh. They are usually small, but may acquire functional activity when pregnancy takes place. Supernumerary nipples may reach as high a number as ten.

3. *The formation in men of breasts* resembling those of women (**gynæcomastia**) is rare in well-developed men with perfect sexual organs (see Hermaphrodism, § 155); but it not infrequently happens that the male breast suffers moderate enlargement at puberty.

4. **Supernumerary bones and muscles** are of frequent occurrence. *Extra vertebræ* may be developed at any part of the spinal column, and, at the lower end, may result in the formation of a **tail**. Besides the true tails containing bones, there are, according to Virchow, two forms of false or imperfect tails, which contain neither bone nor cartilage. One of these forms he regards as a prolongation of the spinal column, while the other he looks upon as a cutaneous appendage of various make-up, which may sometimes be classed with the teratomata. The true tails are very rare, and, according to Bartels, are usually the result of an elongation or separation of the vertebræ rather than of the presence of supernumerary bones.

Supernumerary ribs in the neck or loins, as well as a forking of the ribs, are not rare.

Supernumerary teeth also occur.

5. Within the thorax and abdomen **duplications of the viscera** are most frequent in the spleen, pancreas, suprarenal bodies, ureters, renal pelves, and lungs; they occur more rarely in the ovaries, liver, kidneys, testicles, and bladder.

4. *True and False Hermaphrodism.*

§ 154. The **internal sexual organs** develop from a *primitive sexual gland* lying near the *Wolffian body*, and a *sexual passage*, the *duct of Müller*, which are at first identical in the two sexes. The latter lies close to the Wolffian duct, both terminating in the lower end of the urinary bladder or urogenital sinus (Kölliker).

In the male the duct of Müller nearly disappears, only a trace, the vesicula prostatica or uterus masculinus, remaining; the primitive sexual gland unites with a part of the Wolffian body, which becomes the epididymis, another small portion forming the vasa aberrantia testis (organ of Giraldès), while the chief bulk of the organ disappears, and the Wolffian duct becomes the vas deferens and vesicula seminalis.

In the female the Wolffian body and its duct disappear, leaving only a trace, the parovarium, behind. From the ducts of Müller, which coalesce at their lower ends, develop the vagina, uterus, and Fallopian tubes, the extreme upper end often persisting as a little sac, the hydatid of Morgagni.

The sexual gland first appears in the fifth week. It is produced in mammalia (and probably in man) by a thickening of the peritoneal epithelium, which becomes the germinal epithelium of the organ (Waldeyer), while the mesoderm also proliferates. Whether the seminal tubules are derived from the peritoneal epithelium (Bornhaupt, Egli), or whether they are derived from the Wolffian body (Waldeyer), is still a mooted question (Kölliker). The ova spring from the germinal epithelium. The environing cells of the Graafian follicle are regarded by Waldeyer as also derived from the germinal epithelium, while Kölliker thinks they are probably derived from the Wolffian body.

The significance of the *pedunculate and non-pedunculate hydatids*, situated in varying numbers near the globus major, is not as yet fully determined (Kölliker). According to Waldeyer, the *hydatid of Morgagni* is to be regarded as a remnant of Müller's duct. Roth thinks it may also stand in close relations to the Wolffian body, inasmuch as occasionally a vas aberrans of the epididymis communicates with it.

At first the *testis* lies within the abdominal cavity, in front of and internal to the primordial kidney, close to the lumbar vertebræ. As the primordial kidney disappears, the testis comes into intimate relations with a band of tissue, the gubernacular cord, which passes from the lower end of the primordial kidney to the internal inguinal ring. In the third month of fœtal life the processus vaginalis, a pouch of the peritoneum, pushes its way through the inguinal canal into the scrotum, which is formed from the integument. Meanwhile the gubernacular cord has passed down behind the processus vaginalis into the scrotum, binding the latter to the epididymis, which was formed from a part of the primordial kidney or Wolffian body. Then the testis, covered by peritoneum, follows the course of this band, reaches the internal ring during the seventh month, and at birth is usually situated within the scrotum. The processus vaginalis is obliterated soon after birth, but frequently only imperfectly, and occasionally remains patent.

The ducts of Müller and the Wolffian ducts join in the female to form a single strand. At the end of the second month the ducts of Müller coalesce, at first near their centres and then farther down, to form the *uterus* and the *vagina*. The Wolffian ducts gradually disappear or are represented by mere remnants, situated at birth in the broad ligaments (Kölliker) or in the walls of the uterus (Beigel). Riedel holds that they persist throughout life in about one third of the cases, consisting of a strand of cylindrical epithelium surrounded by muscular tissue, or of a mere muscular bundle lying in front and to the side of the uterus and vagina.

The ducts of Müller at first open into the urinary bladder immediately in front of the Wolffian ducts, while the ureters have their insertions higher up. The lowest portion of the bladder, designated as the urogenital sinus, progresses in its development more gradually than the surrounding structures, which become urethra and vagina; but finally the urinary and sexual organs are so far separated that the vestibule is all that they have in common.

Inasmuch as the vagina develops into a wider channel than the urethra, the urogenital sinus, which at first was a part of the urinary bladder, becomes a continuation of the vagina, into which the smaller urethra opens. The uterus becomes differentiated from the vagina, in the fifth month, by the development of an annular ridge. The hymen is formed from the ridge which marked the junction of the vagina with the urogenital sinus or vestibulum vaginæ.

In the female the gubernacular cord becomes the round and ovarian ligaments. As the Wolffian body disappears, the ovary approaches the inguinal canal and assumes an oblique position. The peritoneal covering of the Wolffian body becomes the broad ligament. As the Wolffian duct disappears, the gubernaculum joins the ducts of Müller, near the point where the Fallopian tube is attached. A processus vaginalis is formed similar to that in the male, but is usually subsequently obliterated; though occasionally the ovary may descend to, and, in extreme cases, be situated in, the labium majus.

The **external genitals** begin to develop even before the separation of the intestinal and genito-urinary orifices, by the formation, in the sixth week, of a median sexual tubercle just in front of the cloaca, and two lateral sexual folds. Toward the end of the second month the tubercle becomes more prominent and its lower surface is furrowed. In the third month the cloaca becomes divided to form the anal and genito-urinal orifices. In the male the genital tubercle develops into the penis, the glans becoming recognizable in the third month, and the furrow closing to form a tube (urethra) in the fourth month. Meanwhile the two genital folds unite to form the scrotum.

The prepuce is formed in the fourth month. The prostate starts in the third month as a thickening of the tissues at the junction of the urethra and sexual passages, its glandular portions springing from the epithelium of the urogenital sinus.

In the female the sexual folds do not unite, but form the labia majora; the genital tubercle becomes the clitoris; the edges of its furrow, the labia minora.

§ 155. The fact that the sexual organs of both sexes develop from structures that are originally common to both, and which contain the beginnings of all the organs of both sexes, makes it *a priori* probable that malformations might result through an unequal development of the organs on the two sides of the body, or through a simultaneous development of organs peculiar to the two sexes, or, finally, through a lack of harmonious development of the external and internal genitalia.

Those malformations in which a single individual acquires sexual organs belonging to both sexes are grouped under the title **hermaphrodism** (Fig. 309). If both sexual glands (testis, ovary) are present the case is designated as **hermaphrodismus verus.** If the combination of the two sexes consists merely of a simultaneous development of male and female genital passages, or of internal organs belonging to one sex and sexual passages belonging to or simulating the other sex, the case is one of false hermaphrodism or **pseudohermaphrodismus.** The true sex is determined by the nature of the essential sexual glands present (ovary, testis).

The bodily habit of hermaphrodites frequently shows a curious blend-

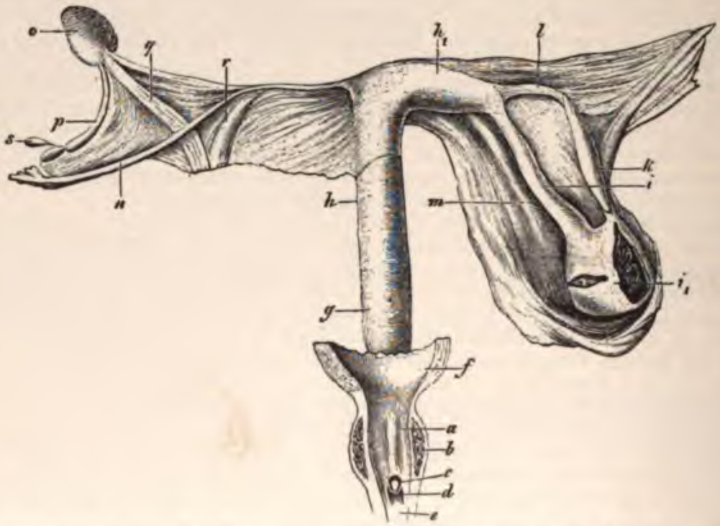

FIG. 309.—Hermaphrodismus verus lateralis. (After Obolonsky.) *a*, Urethra; *b*, Prostate; *c*, Colliculus seminalis; *d*, Hymen; *e*, Urogenital canal; *f*, Bladder; *g*, Vagina; *h*, Uterus; h_1, Left uterine horn; *i*, Left tube; i_1, Infundibuliform extremity of left tube; *k*, Left ovary; *l*, Ovarian ligament; *m*, Left round ligament; *n*, Right tube; *o*, Right testis; *p*, Epididymis; *q*, Right vas deferens; *r*, Right round ligament. (About one-half natural size. Specimen in the pathological collection of the German Pathological Institute in Prague.)

ing of male and female characteristics. For example, the breasts, neck, and shoulders may approach the female type, while a development of the beard, face, larynx, and voice may correspond to the male type. In false hermaphrodites the bodily habitus may by no means always correspond to the true nature of the sex of the individual; a male may resemble a female, and vice versa.

The following **chief forms of hermaphrodism** are enumerated by Klebs:

I. **Hermaphrodismus verus,** or **androgynes.**

Of these there are three possible varieties:

1. *Hermaphrodismus verus bilateralis*, characterized by the presence of both testis and ovary on both sides, or the presence on both sides of a compound organ containing testicular and ovarian structures. According to Klebs, no certainly authentic case of this kind is on record for the human species. Heppner asserts, however, that he found both ovary and testis in the broad ligaments of an individual with hermaphroditic external genitals and possessed of a vagina, uterus, and Fallopian tubes.

2. *Hermaphrodismus verus unilateralis.* Cases in which both sexual glands are present on one side, while only one is present on the other side of the body. No authentic case of this malformation is on record.

3. *Hermaphrodismus verus lateralis.* These are cases in which there is an ovary on one side, a testis on the other. They have been frequently described in human beings (Rudolph, Stark, Berthold, Barkow, H. Meyer, Klebs, Messner, and others), but usually without exact microscopical examination. In the cases where that has been undertaken, ovarian structures had not been made out with certainty until Obolonsky made a histological study of a case in the collection of the German university in Prague, and established the fact of a testis on the right (Fig. 309, *o*) and an ovary (*k*) on the left side. The broad ligament on the right side contained a testis (*o*), an epididymis (*p*), a vas deferens (*q*), a rudimentary tube (*n*), and a round ligament (*r*). The left broad ligament contained an ovary (*k*) with an ovarian ligament (*l*) and a well-developed tube (*i*). There was also a uterus (*h*), vagina (*g*), and a prostate (*b*). According to published observations of cases falling in this class, the sexual passages corresponding to the glands may all be developed or some of them may be lacking. The external genitals are malformed, and combine structures belonging to both sexes.

II. **Hermaphrodismus spurius,** or **pseudohermaphrodismus,** characterized by bisexual development of the external genitals and genital passages, associated with a unisexual development of the essential sexual glands. The most pronounced cases occur in males who, besides their proper sexual organs, possess more or less well-developed vagina, uterus, and tubes. It is much rarer to find that portions of the Wolffian duct have developed in females.

In male false hermaphrodites the external genitals are frequently malformed and approach the female type, while in the female they resemble the male (Fig. 310).

This resemblance is brought about in the male where the penis is stunted, its ventral furrow fails to close (hypospadias), and the two halves of the scrotum remain separate, resembling the labia majora (especially when the testes do not descend), in which case there is usually a depression at the root of the penis between the scrotal halves. In the female the male genitalia are simulated by a development of the clitoris into a sort of penis, a union of the labia, and narrowing or even closing of the ostium vaginæ. The vagina and urethra may have a common opening or separate openings beneath the penile clitoris.

Malformation of the external genitals does not necessarily imply malformations in other portions of the sexual apparatus.

1. *Pseudohermaphrodismus masculinus* occurs in three varieties:

First, *Pseudohermaphrodismus masculinus internus.* The external genitalia belong to the male type, and the prostate is also developed, but is usually pierced, generally at the colliculus seminalis, by a canal which communicates with the urethra and passes above into a rudimentary or more or less well-developed vagina, and occasionally uterus, and even tubes. The male organs may be well developed or more or less malformed.

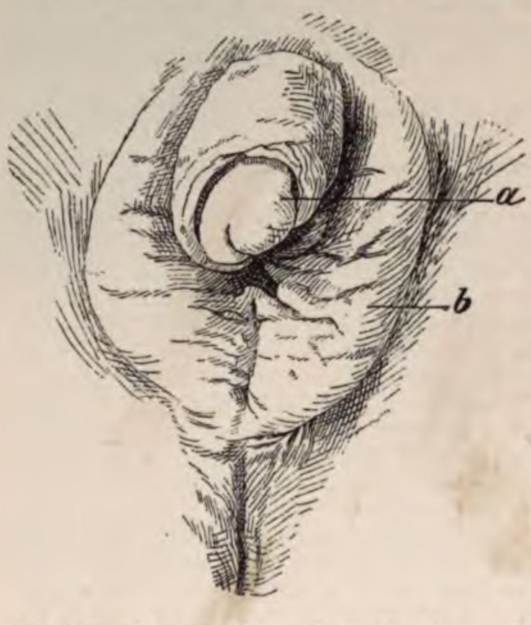

FIG. 310.—External genitalia of a female false hermaphrodite with vaginal stenosis. *a*, Clitoris resembling penis; *b*, Labia majora. (Five-sixths natural size.)

Second, *pseudohermaphrodismus masculinus completus* or *externus et internus.* Vagina, uterus, and tubes are present, either more or less completely developed or in a rudimentary state, and the external genitalia more or less resemble the female type. The penis exhibits the condition of hypospadias resembling the clitoris, and at its root there is usually an orifice leading into a vestibule which divides into a urethra and a vagina. Sometimes the vestibule and vagina are separate. In rare cases the external genitals appear normal, but the penis contains two canals, one, the upper, being the urethra, the other the sexual passage. Where the ducts of Müller are highly developed the vasa deferentia are frequently defective, and sometimes the vesiculæ seminales are wanting.

Third, *pseudohermaphrodismus masculinus externus.* Only the external genitalia depart from the male type, resembling more or less perfectly those parts in the female. As in these cases the bodily habitus often simulates that of the female, they may readily cause a mistake in the sex.

2. *Pseudohermaphrodismus femininus* also occurs in three varieties, but is rarer than masculine false hermaphrodism.

In *pseudohermaphrodismus femininus internus* rudiments of the Wolffian ducts, lying in the broad ligaments or in the uterovaginal walls, and sometimes extending to the clitoris, are found in individuals with well-developed external genitals.

Pseudohermaphrodismus femininus externus is characterized by external genitalia resembling those of the male (Fig. 310).

Pseudohermaphrodismus femininus externus et internus, where the external genitals resemble the male and there is a persistence of parts of the Wolffian ducts, has been recorded in only two cases (Manec, Bouilland, and L. de Crecchio). In one of the cases there was a prostate, in the other a prostate pierced by the vagina, an ejaculatory duct, and a sac resembling a seminal vesicle, which opened into the vagina.

5. *Double Malformations.*

(*a*) *Complete Duplication of the Axial Structures.*

§ 156. **Varieties in which both divisions develop uniformly.**

1. **Homologous twins** result when both divisions develop unhindered. They always are of the same sex, each forming its own amnion, though where the two come in contact an absorption may take place. They possess, almost without exception, a common placenta.

2. **Thoracopagi** are forms in which the trunks—i.e., thoraces and abdomens—are coalescent (Fig. 311). They are also called *omphalopagi*, because they possess a common navel and umbilical cord. Varieties of this malformation are distinguished according to the extent of the coalescence.

Xiphopagi are united only at the ensiform car-

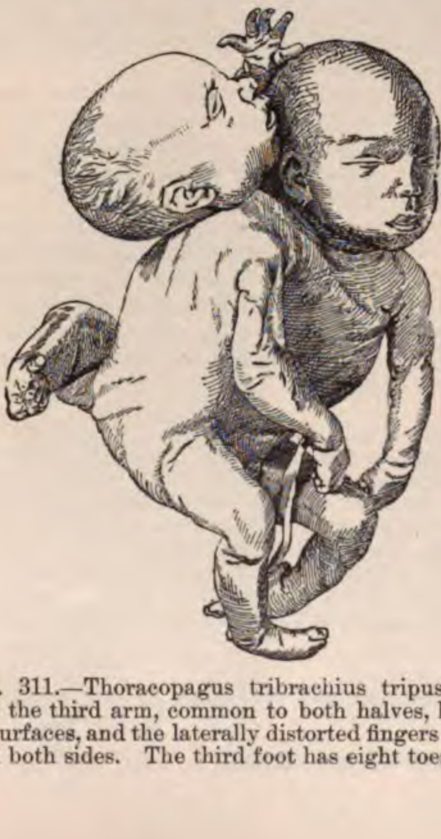

FIG. 311.—Thoracopagus tribrachius tripus. The hand of the third arm, common to both halves, has two dorsal surfaces, and the laterally distorted fingers possess nails on both sides. The third foot has eight toes.

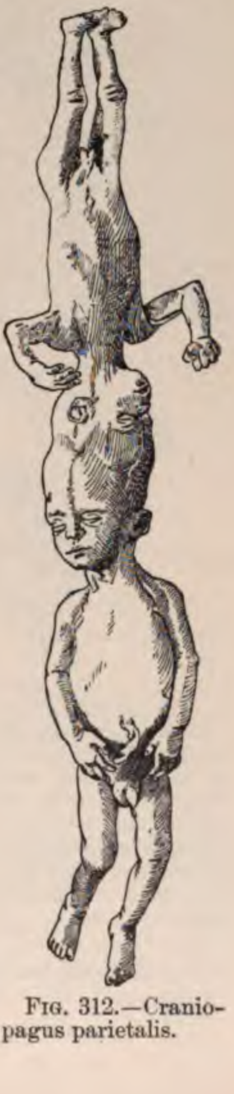

FIG. 312.—Craniopagus parietalis.

tilage by a bridge of that tissue. The peritoneum extends into the bond between the two halves. (The well-known Siamese twins belonged in this division.)

Sternopagi have a common thorax; the sternum is either double or single; the heart also either double or single, but malformed. The intestinal tract is in part common to both halves, in part divided. The liver is double, but the two portions are connected by bridges of hepatic tissue. If of the upper extremities two coalesce, the malformation is designated as *thoracopagus tribrachius* (Fig. 311). If the coalescence involve two lower extremities and the pelvis, it is designated as *thoracopagus tripus*. The coalescence may include not only thorax and abdomen, but also the head (*prosopo-thoracopagus*, or *cephalo-thoracopagus*, or *syncephalus* (Fig. 318, p. 428). Since in these cases portions of the brain and cephalic vertebræ may also be coalescent, they might also be classed with the double malformations with only partial duplication of the axial structures (cf. § 158). The liver of the right twin is usually transposed, which is sometimes the case with the other viscera. The common extremities often show distinct traces of the union of two extremities—e.g., extra toes (Fig. 311) or two dorsal surfaces to the hand (Fig. 311). Thoracopagi are among the most common double malformations.

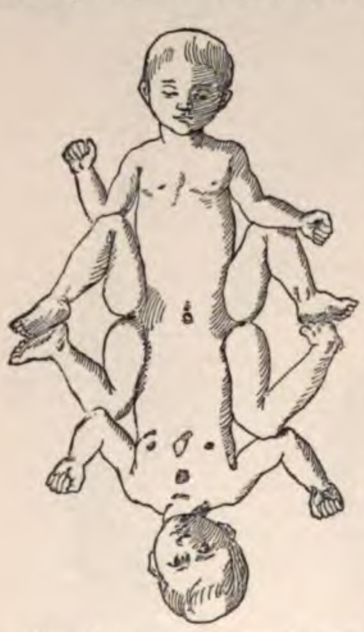

FIG. 313.—Ischiopagus. (From Levy.)

3. **Craniopagi** are twins united by their heads; according to the site of union, they are designated as *craniopagus frontalis, parietalis*, or *occipitalis*. They are rare.

4. **Ischiopagi** (Fig. 313) are united by the pelves. The spinal column and pelvis are duplicate, the latter forming a single wide ring in which the sacral bones stand opposite to each other. This pelvis carries either four or two extremities.

In preparing the classification of double malformations, I have, in the main, followed the work of Ahlfeld,* and the chapters on this subject in Perls's "Allgemeine Pathologie." Förster and Marchand group these malformations into *monstra duplicia catadidyma* or *duplicitas anterior*, *monstra duplicia anadidyma* or *duplicitas posterior*, and *monstra duplicia anacatadidyma* or *duplicitas parallela*. In the last group they include also the parasitic thoracopagi and the rhachipagi. The group duplicitas anterior contains both symmetrical and asymmetrical pygopagi, ischiopagi, dicephalus, diprosopus; and the group duplicitas posterior, the symmetrical and the parasitic forms of craniopagus, syncephalus, and dipygus.

§ 157. Varieties in which the two divisions do not develop uniformly.

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* "Die Missbildungen des Menschen," Leipzig, 1880.

Among these, two groups may be distinguished. In the first group the nourishment of one twin is cut off. It dies without suffering modifications in form. In the second group one of the twins assumes the nourishment of the other; the latter, which is called the *parasite* (while the former is designated as *autosite*), then suffers more or less in its development.

The retrograding parasite may become more or less incorporated with the autosite, or it may be connected with only the placenta of the latter.

The following forms are distinguished:

1. **Fœtus papyraceus.** This form results from a too intimate relationship between the umbilical vessels in the common placenta of distinct twins, where, anastomoses being established, one twin receives nourishment at the expense of the other, which eventually dies. The amniotic fluid then ceases to be formed, and the dead fœtus is compressed by the one which continues to develop, and becomes flat and thin. In other cases the death of one twin may be occasioned by hæmorrhage into the chorionic villi, or by tortion, kinking, or compression of the umbilical cord.

2. **Acardiacus** (Figs. 314 and 315). Malformations in which the heart fails to develop are invariably very imperfect products. The rudimentary fœtus may be connected with the normal twin only by the placenta, or it may be more or less intimately and extensively united with it (cf. Teratomata). In the former case the acardiac fœtus is designated as an *allantoic* or *placental parasite*, and its umbilical vessels communicate with those of its twin, the heart of the latter maintaining the circulation in both. Claudius, Förster, Ahlfeld, and others explain the production of acardi-

Fig. 314.

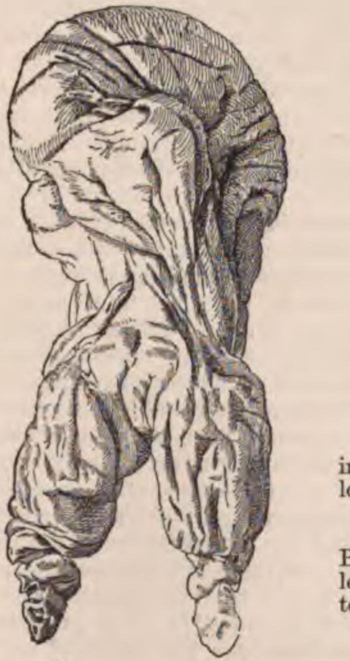

Fig. 315.

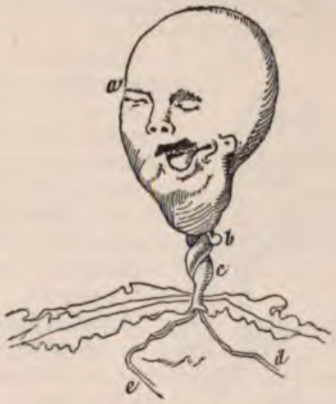

FIG. 314.—Acardiacus acephalus, showing a rudimentary development of the lower extremities (acardiacus amorphus).

FIG. 315.—Acardiacus acormus. (After Barkow.) *a*, Head; *b*, Rudiment of the left upper extremity; *c*, Rudimentary intestine; *d*, Artery; *e*, Vein.

acus by a tardy and insufficient development of the allantois of one fœtus, which, not being able to reach the chorion, attaches itself to the allantois of the other fœtus. The heart, when the blood-current becomes reversed, fails to develop at all, or remains rudimentary. The lungs, trachea, pericardium, diaphragm, sternum, vertebræ, and ribs also fail to develop, or attain only a rudimentary development, which is the case, also, with the liver and upper extremities. The viscera of the abdominal and pelvic cavities usually show the greatest development. The subcutaneous connective tissue frequently attains a marked development, resulting in the formation of irregular masses of tissue (Fig. 314).

Acardiacus occurs in various forms:

(*a*) *Acardiacus amorphus,* which is rare, is an irregular mass covered with skin and containing only rudiments of organs.

(*b*) *Acardiacus acormus.* In this the head is more or less developed (Fig. 315), but the trunk is wanting or rudimentary. It is very rare.

(*c*) *Acardiacus acephalus* (Fig. 314). There is no head; the thorax is rudimentary, while the pelvis and its adnexa are more or less well developed. It is the most common variety of acardiacus. Subvarieties are: acephalus sympus, a. monopus, a. dipus, a. monobrachius, a. dibrachius, and a. paracephalus. The latter possesses a rudimentary skull.

3. **Thoracopagus parasiticus** results when, in a case of thoracopagous twins, one fœtus suffers such deficient development that it forms a sort of appendage to the other. The union includes the ensiform process and that portion of the abdomen extending from it to the umbilicus, and the parasite is therefore frequently designated as *epigastrius.* It rarely possesses a full complement of body parts. In the majority of cases it is an acardiacus acephalus or acormus, whose vascular system blends with that of its host. This malformation is rare.

4. **Epignathus** (Fig. 316) is a prosopo-thoracopagous parasite united to its twin at the mouth of the latter, from which it projects as an amorphous mass of cartilage, connective tissue, glandular and intestinal structures, cerebral tissues, teeth, bone, muscle, and hair-producing skin with an external cutaneous envelope. In very rare cases the epignathus springs from some other site —e.g., the orbit.

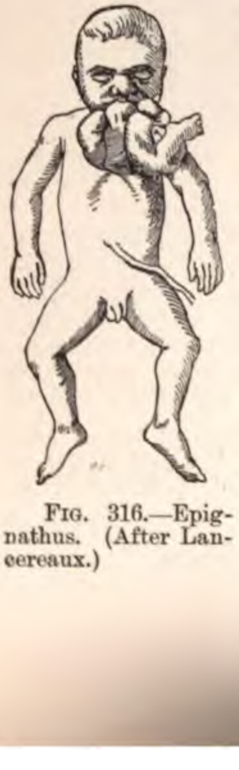
FIG. 316.—Epignathus. (After Lancereaux.)

5. **Teratomata** is the name given to tumors made up of a number of various tissues, this complexity of structure distinguishing them from other neoplasms. Some of them contain rudiments of skeletal parts—e.g., a spinal column, a pelvis, etc. —together with rudiments of various normal organs and tissues, as the intestine, brain, various glands, and nervous and muscular tissues. Others contain various tissues, such as muscle, cartilage, skin, bone, glandular structures, cysts, etc., none of which, however, are so formed or grouped as to represent rudimentary organs or skeletal structures. The former kind are certainly to be regarded as dwarfed parasitic twins (*acardiaci amorphi*) which are intimately united to their hosts. The latter kind are difficult to classify. It is probable that at least some of them are the result of an *erratic*

disturbance in the development of a single fœtus (compare also § 137, on pp. 381, et. seq.).

From this point of view, epigastrius and epignathus are to be regarded as teratomata when they fall short of a certain degree of differentiation and development. Teratomata are most frequently formed at the sacrum (*sacral teratomata*, or *teratoid sacral tumors*). If they resemble a fœtus in their external appearances it is easy to recognize them as the results of twin-formation. The tumor is then called an *epipygus*. The diagnosis is more difficult where the tumor is a shapeless mass, and depends then upon a careful anatomical (and microscopical) study (cf. the preceding pages and § 137). It must not escape attention that just in the sacral region tumors of ordinary connective-tissue types and epithelial tumors are of not infrequent occurrence in the new-born.

6. **Inclusio fœtalis.** The teratomata just referred to often show an intimate union of the parasitic twin with its host. When the teratoid tumors lie more deeply within the substance of the well-developed individual they are designated as *inclusions* and are classified as follows:

(*a*) *Inclusio abdominalis* (*engastrius*).
(*b*) *Inclusio subcutanea.*
(*c*) *Inclusio mediastinalis.*
(*d*) *Inclusio cerebralis* (*teratoma glandulæ pinealis*).
(*e*) *Inclusio testiculi et ovarii.*

Perls regards the views of Claudius with reference to the origin of acardiacus, which have been accepted by Förster and Ahlfeld, as inadequate. He assumes, with Panum,[*] that other factors—e.g., constriction occasioned by the membranes and cord—may cause stunting of one of the fœtuses, in which case, provided there be anastomoses with the vessels of the other normal fœtus, the latter assumes the nourishment of the stunted fœtus. He supports this view on the observation (Orth) that in a single fœtus decapitation may be occasioned in this way.

(*b*) *Partial Duplication of the Axial Structures.*

§ 158. The later in the developmental chain of events a duplication of the axial fœtal structures takes place the less will be the duplication in the resulting product. The most common are duplications at the cephalic end of the fœtus (*terata catadidyma, duplicitas anterior*). Duplication at the caudal end is more rare (*terata anadidyma, duplicitas posterior*). Rarer than either are duplications affecting both extremities of the fœtus (*terata anacatadidyma*).

Duplicitas anterior is most frequently met with in the malformation designated as *diprosopus* (Fig. 317), in which the face is more or less duplicated, as represented by the varieties *diprosopus distomus, diophthalmus, triophthalmus, tetrophthalmus, diotus.* The minimum degree of *duplication* is that of the *hypophysis* (Ahlfeld).

Dicephalus is the name given to cases in which the head and upper end of the vertebral column are duplicated; and, according to the number of upper extremities present, they are specified as *dicephalus dibrachius, tribrachius,* and *tetrabrachius.* The last possesses two hearts and two lungs and is viable. In very rare cases one half remains rudimentary (*dicephalus parasiticus*).

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[*] *Virch. Arch.*, 72. Bd.

If the division of the fœtal structure extends to the pelvis, so that the two halves are united only by the sacrum and coccyx, the resulting production is called **pygopagus.** If twins are united only at some circumscribed portion of the vertebral column, and are separate both anteriorly and posteriorly to that point of union, the malformation is called **rachipagus** or **duplicitas parallela.**

Fig. 317.

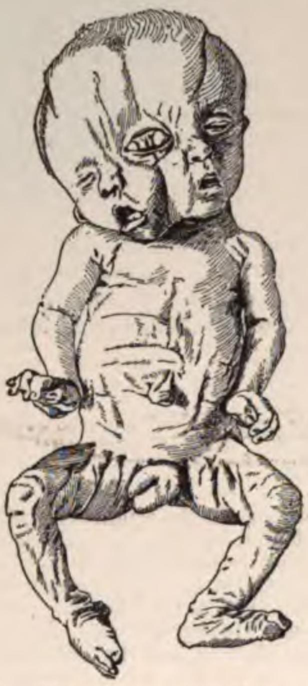

Fig. 318.

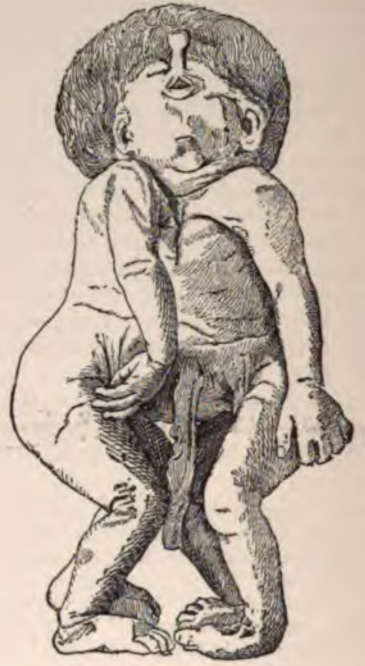

Fig. 317.—Diprosopus distomus tetrophthalmus diotus.

Fig. 318.—Cephalothoracopagus or syncephalus with Janus-head. Both anterior and posterior faces are malformed, having only one eye, and a nose resembling a proboscis situated above the eye.

Teratomata occurring at the sacrum are probably in part rudimentary, acardiac, parasitic pygopagi.

Duplicitas posterior of uniform development is rare in man. In the least marked cases it amounts merely to a duplication of the end of the spinal column, the pelvic bones and organs, and the external genitalia. In more marked cases the lower extremities show more or less duplication. In extreme cases the whole spinal column and back are double, the head uniting the two bodies (*syncephalus*). The head may be simple or show evidence of duplication, such as a double face (*Janus*-head or *Janiceps*, Fig. 318). If, as is often the case, the thoraces are also to some extent united, the Janiceps may be considered as a *cephalo-thoracopagus* (§ 156).

In the higher degrees of division only those axial structures which are situated farthest forward—for example, the brain and cranial vertebræ—remain undivided, and consequently there is no sharp line of separation between syncephalus and a duplication with complete division of the axial structures.

The two faces are usually unequally developed (*Janiceps asymmetros*), and frequently neither is well formed (Fig. 318). If one of the twins is retarded in its growth a *Janus parasiticus* results.

Cases in which there is a duplication of the posterior portion of the spinal column and the pelvis, while the head is simple, are called *dipygus*. A uniform development of the two portions is very rare in such cases, so that *dipygus parasiticus* usually results (Figs. 320 and 321). The parasitic portion is more highly developed the nearer its situation to the cephalic end of the autosite, so that if it have a thorax and upper extremities it usually springs from the mouth, neck, or chest (Fig. 319). If it have only lower extremities they arise from the pelvis (Figs. 320 and 321) (*polymelia*). The parasite is always acardiac and is included in the vascular system of the autosite. The rudiments of the parasite may lie beneath the skin of the autosite, forming a *teratoid tumor*. In very rare cases the duplications are restricted to portions of the pelvis and its contents—e.g., the genitalia and anus.

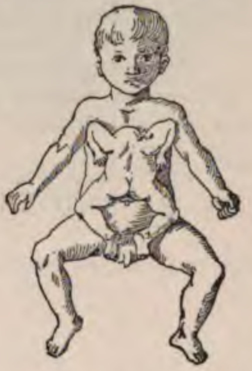

FIG. 319.—Dipygus parasiticus. (After Schenk von Gräfenberg.) Parasite springing from thorax of the autosite.

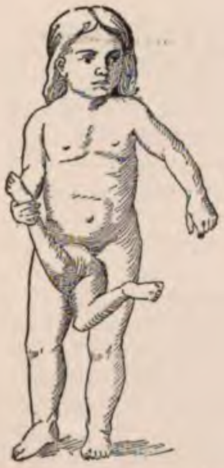

FIG. 320.—Dipygus parasiticus. (After Lancereaux.) Parasite arising from the pelvis of the autosite.

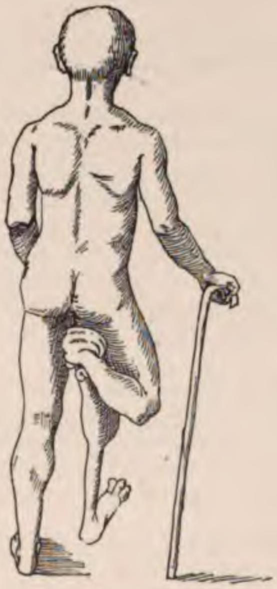

FIG. 321.—Dipygus parasiticus. (After Liesching.)

(c) *Triple Monsters.*

§ 159. Complete division of the germ at the earliest period into several parts may give rise, if development be not checked, to **homologous triplets.** They lie within a single chorion, and there may be either a single amnion, or each fœtus may have its own amnion. Frequently one or two of the triplets are malformed (*acardiacus*).

Where a complete division has taken place and then one of the halves undergoes a further partial division, there are produced within a single chorion *a double monster and a simple fœtus.* This combination is not very rare.

A *three-headed monster* (**tricephalus**) arises from partial division of an already partially divided germ. It is very rare.

SECTION IX.

Fission-fungi which Exist as Parasites and the Diseases Caused by Them.

I. General Considerations in Regard to the Schizomycetes or Fission-fungi.

1. *General Biology of the Fission-fungi.*

§ 160. The **Schizomycetes** or **fission-fungi,** also frequently called collectively **bacteria,** belong to the *protophytes*—i.e., to the very smallest, simplest plants. Many of them are so small that they stand upon the very border-line of invisibility even with the use of the strongest system of lenses. When they occur in animal tissues they are therefore often to be distinguished from disintegrated cell-products of the tissues only with the greatest trouble—i.e., only by the use of different reagents or methods of staining.

The *fission-fungi* throughout are *devoid of chlorophyl and are unicellular organisms,* but they are often found aggregated in smaller and larger colonies.

The form and character of the individual cells, as well as their growth, their division and reproduction, are different, and at present these differences are used to group the bacteria into different genera. The **cocci,** often also called micrococci, constitute the first genus of fission-fungi, and constantly occur as spherical or oval cells, and were formerly often called *sphærobacteria* (Cohn). Six forms of growth can be distinguished according to their grouping in the process of reproduction: *double cocci* or *diplococci, chain-cocci* or *streptococci, clustered cocci* or *staphylococci, tablet-formed cocci* or *merismopedia, packet-shaped cocci* or *sarcinæ,* and *tubular cocci* or *ascococci.*

The **bacilli** (rod-shaped bacteria) form the second class, which was formerly divided by Cohn into *microbacteria* and *desmobacteria,* according to the length of the rods. Along with the designation *bacillus* many authors employ the name *clostridium* for bacilli which assume spindle and club shapes in the formation of spores. Long threads are also often called *leptothrix.*

The **spirilla** (screw-like coiled rods) form the third genus. Screws with short, wide turns are called *spirilla,* those with drawn-out turns *vibrios,* those with a long, narrowly twisted screw *spirochaete.*

All of the bacteria as yet referred to occur either in one single form of growth or in a very limited cycle of forms of growth, and may therefore be grouped together as **monomorphic** or **oligomorphic bacteria.**

Cohn, to whom we are indebted for the fundamental investigations of the bacteria, united under this term exclusively these oligomorphic organisms.

Recently, however, there have been also organisms classified as bacteria which have in their ontogenesis a long series of forms of growth—i.e., forming spherical cells as well as rods and screws—which can be consequently called **pleomorphic bacteria.** Here belong, namely, the water-fungi which go by the names *cladothrix*, *beggiatoa*, and *crenothrix*.

The fission-fungi are all made up of a plasma, or **cell-contents,** surrounded by a **cell-membrane,** both, according to Nencki, consisting for the most part of an albuminous substance, or **mycoprotein.** According to observations of Schottelius and others, it is possible with good lenses to differentiate in the inside of the bacilli oblong bodies, in the inside of cocci round bodies, which are probably to be interpreted as **cell-nuclei.** These bodies differ optically from the cell-protoplasm, and divide in two before the division of the cell takes place. According to Nägeli, Zopf, and others, many fission-fungi possess a membrane consisting of cellulose, or at least of a carbohydrate very nearly resembling cellulose. This membrane becomes turgid under certain conditions of growth in many of the bacteria, and forms a *capsule* having a hyaline appearance.

In all forms of the bacteria except the cocci wandering **motion** has been observed, which is brought about by means of fine **flagellate threads** in lively vibration. In addition there is a slow oscillatory or a gliding and creeping motion carried on by the contractile and flexile plasma. Both forms of motion appear only under certain conditions of nutrition and growth and only in certain species.

Multiplication of the bacteria takes place by **transverse division** of the cell, which previously grows out longitudinally. In some forms division can take place in two or even in all three dimensions of space. After division the cells separate immediately or remain for a time hanging together. If they hang together after dividing according to the first method, they **form threads** (*streptococci*, *leptothrix*); according to the second method, **colonies in a plane are formed** (*merismopedia*); according to the third method, **colonies are formed in a solid body** (*sarcinæ*). Long threads can become segmented into shorter pieces.

According to the investigations of Buchner, Longard, and Riedlin, the period of reproduction—i.e., the length of time from one cell-division to the next—in the cholera-spirillum under favorable conditions of nutrition varies from fifteen to forty minutes.

If the bacteria in the period of rest aggregate into clumps in consequence of constantly progressing reproduction, or by the accumulation of neighboring cells anywhere in great masses, there are often formed glutinous colonies which are called **zoöglœa.** The jelly is formed out of the cell-membranes of the fission-fungi, and, according to Nencki, also consists of mycoprotein. The glutinous masses can assume the most various shapes, and reach at times a considerable size, forming clumps or patches or ropes of from one to three or more centimetres in diameter.

Under certain circumstances many of the fission-fungi form **spores.** These are cells which are distinguished by the fact that they remain alive under conditions in which the ordinary vegetative forms die; and moreover, when they are put into fresh nutrient solutions, they can produce a new generation. Most frequently the *spore-formation is endogenic*—i.e., the spore arises inside of a cell, especially in bacilli, and is developed out of the protoplasm of the cell. In the latter a small granule appears, which grows out into an oblong or round, highly refractive, sharply contoured body, always remaining smaller than the mother-cell. The spore becomes free after the disintegration of the mother-cell. The formation of *arthrospores*, observed in micrococci, is said to take place by the assumption directly of the characteristics of spores by individual members of a colony or of one of the series of generations, while at the same time they either remain externally unaltered or take on other morphological peculiarities.

Babes and Ernst, by special methods of staining with Löffler's methylene blue, hæmatoxylin, and Platner's nuclear black, have found in the interior of different bacteria, granules which, according to their behavior, probably bear some relation to the cell-division and to the spore-formation. Ernst designates the bodies found by him as *sporogenic granules*, since he was able to trace in some bacteria the transition of these into spores. He is inclined to attribute to them the nature of a cell-nucleus, a view assented to by Bütschli.

§ 161. The fission-fungi, owing to the absence of chlorophyl in them, are restricted in their **nutrition** entirely to ready-formed **organic substances** which are soluble in water and which are supplied to them in an abundance of **water.** They need, moreover, **various mineral substances,** especially sulphur, phosphorus, potassium or rubidium, or cæsium and calcium, or magnesium or barium or strontium.

They are capable of taking their necessary *carbon* from most of the carbohydrates that are soluble in water. They can derive their carbon from dilute solutions of compounds which in greater concentration are destructive, as, for example, benzoic acid, alcohol, salicylic acid, phenol, etc.

The fission-fungi derive their *nitrogen* from *albuminous matter;* moreover, from those compounds which are designated as *amines* (methylamine, ethylamine, propylamine), *amido-acids* (asparagin, leucin), and *amides* (oxamide, urea); and also from the *ammonia salts,* and partly also from *nitrates.* The albuminates are changed into peptones, previous to their assimilation, by a ferment given off from the fission-fungi. Free nitrogen cannot be assimilated as such. Nitrogenous and non-nitrogenous compounds are not only assimilable as such, but also in combination. The fission-fungi can derive their nitrogen from ammonia and nitric acid only in the presence of organic carbon compounds.

According to Nägeli, *sulphur* is essential to the fission-fungi, and they take it from sulphates, sulphites, and hyposulphites. They take the other *mineral substances* enumerated above from various salts. If along with abundance of nutrient material there is too little water present, all further growth ceases; still many fission-fungi are able to dispense with water temporarily. Spores suffer very little from the effects of drying.

Some of the fission-fungi are restricted, for their nourishment, mainly or exclusively to dead organisms or to solutions of organic matter, and belong, therefore, to the **saprophytes.** Others are also able to derive their nutrition from living animals or plants, and are therefore to be reckoned among the **parasites.**

If the fission-fungi get into water containing no nutritive material, many of them die in time. The spores resist the longest in this respect.

Free **oxygen** is necessary for the growth of many bacteria; others can dispense with it so long as they are under favorable conditions in other respects; still others develop only where oxygen is cut off. The first of these are called *obligatory aërobes*, the second *facultative anaërobes*, the third *obligatory anaërobes.*

Facultative anaërobes produce in part fermentation by their multiplication in the absence of oxygen; but, according to the investigations of Flügge and Liborius, fermentative phenomena seem also often to be absent. Pathogenic bacteria, according to Liborius, are facultative or obligatory anaërobes.

Carbon dioxide has no influence upon the development of many bacteria, as, for example, upon the typhoid-fever bacilli and upon the Friedländer pneumonia-bacilli. Upon others, on the contrary, it has an inhibitory action, as, for example, *Bacillus indicus*, *Proteus vulgaris*, and *Bacillus phosphorescens*, the bacilli of anthrax and of cholera, the pus-cocci, and others (C. Fränkel). The bacilli of anthrax, of cholera Asiatica, and of rabbit septicæmia die out in a few hours in artificial Seltzer water, but the spores of anthrax-bacilli keep alive indefinitely (Hochstetter).

Intense **light** has an injurious or destructive effect upon the development of many bacteria, and consequently infected water can be disinfected by light (Buchner). In *Bacillus anthracis* the virulence can be weakened by sunlight (Arnold, Gaillard). Anthrax-spores die out when exposed for a long time to light and air (Arloing, Roux). According to Geisler, the green, violet, and ultra-violet are the rays which are particularly injurious to them.

According to Nägeli, Hauser, Buchner, Zopf, and others, *different conditions of nutrition act in modifying the form and dimensions of the fission-fungi.* For example, bacilli cultivated in different nutrient solutions have different lengths as well as different thicknesses. In many varieties, moreover, it is said that, in one nutrient solution, the change is generally into spherical cells and short rods, while in another, on the contrary, it is into long threads (Zopf). Finally, the *physiological properties can also change under different modifications of nutrition.*

The **temperature** of the medium surrounding the bacteria acts generally in such a way that when there is a fall the vital processes become weaker and slower, and finally cease, whereas with elevation of the temperature they rise to a certain maximum, and at a slight excess above this suddenly cease; still higher temperatures kill the fungi. The maximum of permissible temperature lies at a different height for different fungi, and, according to Nägeli, is also partially dependent upon the character of the nutrient substance.

A low temperature stops development in all. They fall into a state of numbness, but do not die even at very cold temperatures. The rigidity due to cold develops in the individual forms at different temperatures. The most favorable temperature for the *Bacillus anthracis* lies between 30° and 40° C.; at temperatures above 44° C. and below 15° C. there is cessation of development. Many bacilli form spores only at high temperatures.

Boiling water and *steam* at 100° C. kill all bacteria and bacterial spores if allowed to act for some time. Bacteria and their spores bear higher temperatures in dry air, so that a temperature of 140° C. for three hours is necessary to kill the latter. Many bacteria are killed at a temperature of 60–70° C., provided it be kept up for a very long time.

Anthrax-bacilli multiply within certain limits more and more slowly the lower the temperature is. Between 30° and 40° C. growth and spore-formation usually cease at the end of twenty-four hours. At 25° C. the time required rises to from thirty-five to forty hours. At 23° C. forty-eight to fifty hours are required for the spore-formation; at 20° C., seventy-two hours. At 18° C. spores appear at the end of five days; at 16° C., after seven days. Below 15° C. all growth and spore-formation cease (Koch). Spore-formation still takes place even at 42° C.

In hot dry air, bacilli free from spores do not withstand a temperature a little over 100° C. for an hour and a half. In hot dry air, spores of the bacilli are destroyed at a temperature of 140° C. at the end of three hours. The temperature penetrates the objects to be disinfected so slowly in hot air that objects of moderate dimensions, such as a small bundle of clothes, pillows, and such things, are not disinfected after three or four hours' exposure to a temperature of 140° C. (Wolffhügel).

Anthrax-spores die in *boiling water* in two hours, in *confined steam* in ten minutes; but the spores of the garden-earth bacillus (garden-earth contains usually a peculiar bacillus) are not killed in this time. The action of steam at 105° C. for a period of ten minutes kills all spores.

Watery vapor is more effective when in motion than when it is confined. It then kills all spores in from ten to fifteen minutes, and penetrates very well into the objects to be disinfected (Koch, Gaffky, Löffler). In disinfecting with boiling water, attention must be well given that the heating lasts a long time—i.e., till all parts are heated up to 100° C.

According to Arloing and Duclaux, anthrax-bacilli die in from twenty-four to thirty hours when exposed to the direct rays of the sun; spores in from six to eight weeks.

§ 162. If fission-fungi find themselves in a medium which suits them, their multiplication can still be brought to a standstill provided the fluid contain **substances which hinder their growth or even kill them.** This effect is produced by many substances—sublimate, lysol, carbolic acid, iodine, etc.—even in comparatively great dilution. Other substances operate injuriously upon the bacteria only when they are in stronger concentration. The point at which the multiplication is hindered is always reached at much greater dilution than that at which the bacteria are killed. Spores are much more resistant than the vegetative forms.

Many bacteria are very sensitive to acids, so that even a small degree of acidity hinders the growth. This is true, for example, of the organism of anthrax and of the Fränkel-Weichselbaum pneumococcus. But still some are able to grow with a moderate amount of acid in the nutrient fluid. As a general rule they are specially sensitive to the mineral acids, but the presence of a large amount of citric, butyric, acetic, and lactic acid also hinders the multiplication. In this connection belongs the fact that the products of decomposition caused by the fermentative action of the fungi at a certain degree of concentration are injurious to the development of the fungi, and finally stop their growth entirely. Thus in butyric-acid and lactic-acid fermentation the quantity of butyric acid and of lactic acid gradually formed may finally cause cessation of the growth of the fungus. A similar result occurs in the bacterial putrefaction of albumin, since the products, such as phenol, indol, skatol, phenyl acetic acid, phenyl propionic acid, etc., hinder the further development of the bacteria. The fission-fungi are less sensitive to alkalis, and many of them can bear a tolerably high degree of alkalinity in the nutrient fluid; but, on the other hand, there are certain forms which do not flourish in alkaline fluids—e.g., acetic-acid fungus.

Multiplication also ceases in the presence of a superabundance of nutrient material—i.e., with an **insufficient amount of water.** The fact that fruit preserved in sugar, and salted and dried flesh, do not become foul depends upon this. Food-stuffs can also be preserved by depriving them of water and by the addition of substances which are dissolved in the tissue-fluids, and in this way increase the proportion of solid matter. The limit at which development takes place is reached at a much higher degree of humidity for the fission-fungi and yeast-fungi than for mould-fungi.

According to investigations of Pfeffer and Ali-Cohen, many motile bacteria show chemotactic properties—i.e., they are attracted or repelled by chemical substances dissolved in water. The bacteria swimming around in the fluid consequently collect together at places where there are chemical substances which attract. Typhoid-fever bacilli and cholera-spirilla, for example, are attracted by the juice of a potato (Ali-Cohen). Potassium salts, peptone, and dextrine also act by attraction, but the individual bacteria behave differently toward these substances (Pfeffer). Free acids, alkalis, and alcohol have a repulsive action.

If a nutrient fluid contains other lower fungi besides the bacteria there often takes place a **competition between the different micro-organisms,** and fission-fungi, budding fungi, and mould-fungi can crowd one another out.

If, for example (Nägeli), fission-fungi, yeast-fungi, and mould-fungi are introduced together into a solution of sugar, the fission-fungi alone increase and cause lactic-acid fermentation. If to the same solution 5 per cent. of tartaric acid is added, the budding fungi alone multiply and cause alcoholic fermentation. If 4 or 5 per cent. of tartaric acid is added, only the vegetation of mould is obtained. The addition of the tartaric acid does not make the life of the other fungi impossible, but only favors the development of one over the other. In the same way the budding fungi alone develop in grape-juice, although other germs find their way into it, and the fission-fungi can only multiply and produce acetic acid after all the sugar is used up. Mould-fungi, which destroy the acid, can develop on the vinegar. Subsequently fission-fungi again appear and produce putrefaction.

Often a large number of fission-fungi develop in one culture-fluid, and it often seems as if they favored one another's growth; still a **reciprocal crowding out occurs** among the fission-fungi themselves. Thus, for example, cocci can be supplanted and destroyed by bacilli, or one form of bacillus by another. This would happen where either the composition or the temperature of the nutrient fluid is more favorable for one or for the other, or also where one species of bacteria forms products which act injuriously upon the other, or where one form grows more rapidly than the other and in this way takes away the necessary nutrient material from the competitor.

According to the investigations made by Pasteur, Emmerich, Bouchard, Woodhead, Blagovestchensky, and others, the antagonism between many bacteria shows its influence even in inoculation experiments upon animals. By simultaneous inoculation with different bacteria it sometimes happens that the development of a pathogenic fission-fungus in the body of a susceptible animal is hindered. Thus, for example, the development of the anthrax-bacillus can be hindered by a simultaneous inoculation with erysipelas-cocci (Emmerich) or with the *Bacillus pyocyaneus* (Bouchard).

Substances which are specially adapted to hinder the growth of the bacteria, or to kill them, are usually called **antiseptic substances.** The knowledge of their action is of great practical interest, as it is possible in this way with their aid to render solid or fluid bodies and also human tissues free from bacteria, or at least to hinder the development of bacteria in them and so to protect the body in question from the injurious action of the bacteria. For therapeutic and hygienic purposes, *sublimate, lysol, carbolic acid,* and *preparations of iodine* are the antiseptics chiefly used.

§ 163. *The growth and multiplication of the fission-fungi are uniformly accompanied by considerable changes in the tissues or fluids upon which they feed.* For not only is material taken away by osmosis and used to build up new fungus-cells, but at the same time **extensive destructive chemical metamorphoses** take place, which affect the assimilated substances, as well as also the substances outside the cells, and lead to a decomposition of the complicated organic compounds into simpler bodies. These metamorphoses are due to the vital activity of the protoplasm, and can be regarded as **fermentation processes.**

As to whether the decomposition in fermentation takes place inside the cells or on their surface is not yet decided, but the latter is the more probable.

In the decomposition caused by the fission-fungi there are numerous products formed, which vary according to the character of the nutrient fluid and the form of the fission-fungus. A fission-fungus can only produce fermentation when an adequate fermentative material is present for it. Many fungi can do this as well in the presence as in the absence of oxygen. In some of them paucity of oxygen is essential. Fermentation is unknown in some of the fission-fungi.

The fermentations caused by the fission-fungi constitute essentially much of the decomposition going on every day on a large scale. Thus, for example, they are the cause of the *stinking putrefaction of albumin;* they *change milk into lactic acid (sour milk); mannite, dextrine, glycerin, sugar of milk, starch, and lactic acid into butyric acid (fermentation of sauerkraut); sugar into a gummy slime (so-called "langer Wein"); alcohol into acetic acid; urea into carbonate of ammonia.*

In the **putrefaction of albumin, peptones** and similar bodies are first formed; then afterward **alkaloidal bodies,** so-called **ptomaines,** as, for example, the putrid poison of Panum, sepsine (Bergmann, Schmiedeberg), collidine (von Nencki), peptotoxin, neuridine, neurine, choline, tetanin, ethylendiamine, cadaverine or pentamethylendiamine, putrescine or tetramethylendiamine, substances resembling gadinin and muscarine (Brieger); then next, **nitrogenous bases:** leucin and tyrosin, amine, methyl-, ethyl-, and propylamine; moreover, **organic fatty acids:** formic acid, acetic acid, propionic acid, butyric acid, valerianic acid, palmitic acid, margaric acid, lactic acid, succinic acid, etc.; furthermore, **aromatic products:** indol, phenol, cresol, pyrocatechin, hydrochinon, hydroparacumaric acid, and para-oxyphenyl acetic acid (von Nencki, Salkowski, and Brieger); finally, sulphuretted hydrogen, ammonia, carbon dioxide, and water. Besides the bodies enumerated above, there result from the growth of numerous pathogenic bacteria albuminous bodies which act in a poisonous manner upon the human and animal organism, and are therefore called **toxalbumins.**

The products named are formed partly by hydration, partly by reduction, partly by oxidation.

Along with the fermentative action the fission-fungi also give off dissolved substances which produce decomposition, are known as **unformed ferments,** and may be separated from the fungi. The unformed diastatic ferments convert starch and cane-sugar, and perhaps, also, lactose and cellulose, into grape-sugar, and the insoluble peptone-producing albuminous substances into peptone. In consequence of this, milk may undergo an alcoholic fermentation, and insoluble albuminoid masses may undergo putrefaction.

According to the investigations of Winogradsky, there are also *living bacteria in the soil which are able to form nitrous and nitric acid out of ammonia; and he calls these, accordingly, nitrifying* or **nitro-bacteria.** Along with the nitrification of nitrogen there takes place simultaneously a destruction of the earthy alkali carbonates, as shown by the fact that the nitrobacteria are able, in the absence of organic carbon compounds, to derive the carbon necessary for the building up of their cells from the *salts of carbonic acid.* There takes place, therefore, as a result of the vital activity of these organisms, a synthesis of organic material out of inorganic substances.

Under the influence of the fission-fungi there are formed **bitter, sharp, disgusting substances** that are but little known. Milk that has become bitter affords an example of this. Furthermore, they occasionally produce **pigments** of red, yellow, green, blue, and violet color. Thus, for example, a blood-red coating of *Bacillus prodigiosus* forms on bread (bleeding bread); moreover, bandages and pus sometimes turn blue in consequence of the presence of the *Micrococcus cyaneus.* On the surface of boiled eggs exposed to the air in a moist place there appears usually very quickly a yellow coating, formed by the *Micrococcus luteus.*

The **phosphorescent phenomena** to be seen not infrequently on putrefying sea-fish depend also upon bacterial products of decomposition, as proven by Pflüger, and appear where there is a lively reproduction of the bacteria.

Fermentation and putrefaction can only occur where the fungi concerned live, and the extent of the decomposition is conditioned upon the number of fungi. One specific fungus form does not occur alone in every decomposition, and a single fungus form often causes not alone one kind of decomposition. The ordinary stinking putrefaction of albuminous substances develops under the influence of different bacteria, but especially under that of Proteus. According to Cohn, the cocci do not produce putrefaction, but decompositions of another kind. Butyric-acid fermentation is said to be brought about mainly by the *Clostridium butyricum.* Anthrax-bacilli produce ammonia in nutrient fluids. In putrefying substances are found, for the most part, many kinds of fission-fungi.

According to Nägeli, it is possible by cultivation to change the properties of a fission-fungus in such a way that it will no longer be able to bring about the decompositions which it previously caused, but it will cause some other fermentation. According to him, it is possible, for example, to change by cultivation, in meat-extract containing sugar, the fission-fungus which causes lactic-acid fermentation in such a way that when it is reintroduced into milk it causes an ammoniacal decomposition, and it only regains the power of producing lactic acid after many generations. Accordingly the physiological properties of a fission-fungus are capable of a change within certain limits; or, at least, with changes in the conditions of life, different properties predominate.

The first investigations to establish the changes characteristic of putrefaction were made by Th. Schwann and Franz Schulze,* in the middle of the fifties, and upon the results of their experiments they expressed the opinion that fermentation and putrefaction depend upon the presence of very small organisms. Almost at the same time (1857) Cagnard-Latour observed the multiplication of yeast-cells in alcoholic fermentation. The observation made by Schwann was subsequently corroborated by Helmholtz. H. Schroeder and von Dusch then showed that by filtering through cotton-wool the air admitted to a fluid capable of fermentation, and also by the action of higher temperatures, the appearance of fermentation may be hindered.

Since the investigations of Schwann there have been advanced many hypotheses upon the cause of fermentation, especially upon the alcoholic fermentation caused by the yeast-fungi. Certain authorities have sought to bring these processes in immediate relationship to the life of the cells causing the fermentation; others have sought to separate them from the latter. According to Liebig, the process is due to a molecular movement which an unformed ferment or a body in a state of chemical activity—i.e., decomposing—imparts to other bodies whose elements are not held strongly together. According to Hoppe-Seyler and Traube,† the cells excrete certain substances, so-called unformed ferments, which cause decomposition by contact action—i.e., merely by their presence, without taking part chemically or entering themselves into a compound.

According to Pasteur,‡ fermentation is dependent directly upon the life of the fermentative cells. It only occurs when free oxygen is lacking to the cells, so that these have to take the oxygen from the chemical compounds in the nutrient fluid (cf. § 161). In this way the molecular balance of the latter is destroyed. According to von Nencki, also, anaërobiosis is to be regarded as the cause of the different kinds of fermentation. Since the fermentative organisms derive their oxygen not out of the air, but out of the nutrient substance, there appear constantly also reduction products—alcohol, butyric acid, etc.—along with the end-product, carbon dioxide.

According to Nägeli's *molecular-physical theory*,§ fermentation is a transfer of molecular motion from the living protoplasm to the material undergoing fermentation. This motion is present in the molecules, groups of atoms, and atoms of all substances. The compounds forming the living protoplasm remain themselves unchanged, but by the transfer of molecular motion they destroy the equipoise in the molecules of the fermenting substance, and these become disintegrated.

The power to produce fermentation—i.e., decomposition—in the nutrient fluid is very likely not only a property of fission-fungi and yeast-fungi, but also of the cells of more highly organized beings, therefore also of man. According to Voit,‖ the decomposition of the dissolved albumin circulating in the organism is attributable to a fermentative activity of the cells. Pasteur has shown that fruit and leaves possess fermentative properties under suitable conditions.

As already remarked, the amount of oxygen present has considerable effect upon the decomposition caused by fission-fungi. Pasteur states that fungi that grow in the presence of oxygen produce principally oxidation; those, on the contrary, that grow without oxygen produce decomposition without oxidation. Hoppe-Seyler ¶ corroborates the fact that the presence of an abundance of oxygen retards the decomposition of sugar into alcohol and carbon dioxide by yeast, while at the same time volatile acids are formed in abundance. If bacteria develop in an albuminous fluid with abundant access of oxygen, all of those substances vanish which constitute an important part of the products of decomposition in the presence of a paucity of oxygen—namely, indol, hydroparacumaric acid, sulphuretted hydrogen. The oxygen must therefore act by inducing oxidation, and the products of fermentation suffer further changes.

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* *Poggend Annal.*, 29. Bd., ref. in *Schmidt's Jahrb.*, 1866.

† Cf. Hoppe-Seyler, *Pflüger's Arch.*, 12. Bd., 1875, and "Physiol. Chemie."

‡ *Ann. de Chim. et de Phys.*, tome 58, 1860, et tome 64, 1862; *Comptes rend. de l'Acad. des Sciences*, tomes 45, 46, 47, 52, 56, 80; and Duclaux, "Ferments et maladies," Paris, 1882.

§ *Abhandl. d. Bayr. Akad., Math.-physik. Kl.*, iii., 76, 1879.

‖ "Physiologie des Sauerstoffwechsels," Leipzig, 1881.

¶ "Ueber den Einfluss des Sauerstoffes auf Gährungen," Strassburg, 1881.

Along with fermentation and putrefaction which result from fungi, there are other decompositions of organic substances in the production of which the fungi have no part. These consist mainly in a slow oxidation or burning, in which carbon dioxide and water are formed, and, in the case of nitrogenous substances, also ammonia. This form of decomposition takes place under conditions where atmospheric air and moisture are in contact with organic matter. Moreover, it also takes place in the living organism. In dead organic matter this answers partially to the process usually called *mouldering*.

2. *General Considerations concerning the Pathogenic Fission-fungi and their Behavior in the Human Organism.*

§ 164. As has been already explained in §§ 13 and 14, there are among the fission-fungi numerous species which are capable of producing disease processes in the human organism, and they are therefore called **pathogenic fission-fungi.** The first condition of such action is evidently that the bacteria concerned must possess properties enabling them to multiply in the tissues of the living human body. They must consequently find in the tissues the suitable nutrient material, and in the body-temperature the warmth, necessary to their growth. The tissues, moreover, must not contain substances which are a hindrance to their growth (cf. §§ 26 and 29).

If pathogenic fission-fungi succeed in growing in the tissues of the body—i.e., if **infection** takes place (cf. § 14)—their action is in general characterized, at the point of multiplication, by *degeneration* (Fig. 322, *c*), *necrosis*, *inflammation* (*e*), and *new growth of tissue*, while the *toxins* and *toxalbumins* produced by them *cause manifestations of poisoning*.

But in individual cases the disease process assumes different forms,

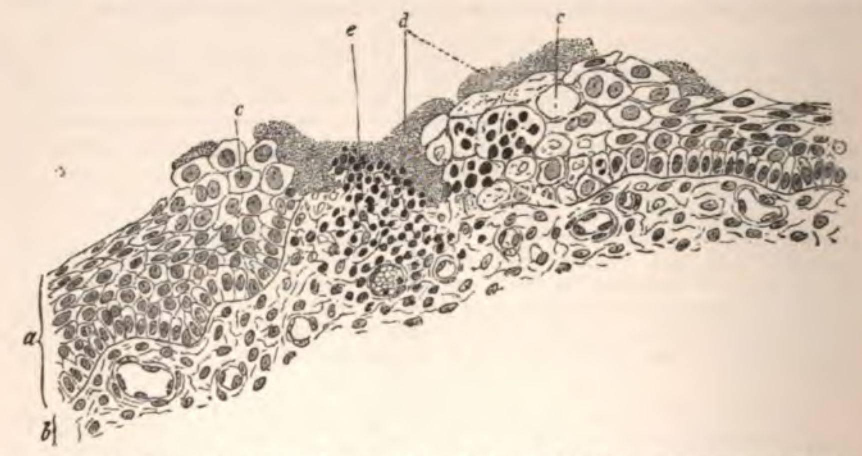


FIG. 322.—Section through a vocal cord of a child with streptococcus colonies upon and in the epithelium. *a*, Epithelium; *b*, Connective tissue of the mucous membrane; *c*, Swollen, degenerated epithelium, in part devoid of nuclei; *d*, Layer of cocci; *e*, Reactive small-cell infiltration, partly inside the degenerated epithelium, partly in the connective tissue. (Magnified 200 diameters.)

in that the distribution of the bacteria in the organism and their local action, as well as the production of poisons, differ greatly in the different forms of bacteria.

In many of them the local action upon the tissues comes to the front; in others the general intoxication. Many bacteria confine themselves to the region in which they have found entrance; others advance uninterruptedly into the surrounding neighborhood; still others are carried by the lymph- and blood-currents and lead to the formation of metastatic foci (cf. § 18); and finally, still others increase in the blood.

If a spread of the bacteria takes place through the blood, the *bacteria may go from the mother to the fœtus* during pregnancy, since the placenta forms no certain filter against pathogenic bacteria.

This has been proved, for example, for anthrax-bacilli (Straus, Chamberland, Marchand, Malvoz, Latis, Birch-Hirschfeld, Perroncito), for the bacilli of symptomatic anthrax (Arloing, Cornevin, Thomas), for the bacilli of glanders (Löffler, Mallet, Cadéac), for the spirilla of relapsing fever (Albrecht, Spitz), for the bacilli of typhoid (Eberth, Neuhauss, Reher, Chantemesse, Widal, Ernst), and for the pneumococcus (Netter, Foà, Bordoni-Uffreduzzi). According to certain observations of Malvoz, Birch-Hirschfeld, and Latis, changes in the placenta, such as hæmorrhages, loss of epithelium, alterations of the vessel-walls, favor the transmigration of the bacteria. Bacteria—as, for example, anthrax-bacilli—can grow through the tissues. The passing over of bacteria from the mother to the fœtus presupposes, as a rule, that after the entrance of these organisms into the circulating blood of the mother, the latter shall remain alive at least long enough to allow of the transmigration.

The *bacteria* which succeed in multiplying in the human body *die out again, in many cases, in a short time*, and the diseases caused by them proceed to *recovery* (cf. § 27). Nevertheless it also not infrequently happens that *they are preserved for a long time in the body*, and either continuously *cause disease processes*, or, on the other hand, remain in a state of inactivity, so that no disease processes of any kind are recognizable *till, after a shorter or longer period of latency, a lively multiplication takes place*, and along with it *new manifestations of disease show themselves*.

Not infrequently a **secondary infection** associates itself with an infection already existing. The relation between the two infections is either that the second occurred accidentally after the first became established, or, on the other hand, that the way was prepared by the first infection for the subsequent one (cf. § 14).

Finally, **double infection**, where two or even more forms of bacteria come to development in the tissues simultaneously and exert their destructive influence upon them, is not an infrequent occurrence.

§ 165. Each pathogenic fission-fungus has a **specific action** upon the tissues of the human body; but, nevertheless, *different species of fission-fungi may exert similar action*. Thus, for example, various bacteria can cause suppuration. Consequently it is only in a certain proportion of cases that the morbid changes in the tissues are so characteristic that the species of the pathogenic fission-fungus can be recognized with certainty.

It has been demonstrated, moreover, that **the pathogenic properties of the bacteria are not entirely constant**; that, on the contrary, their virulence varies, so that bacteria that cause severe or fatal infection may become changed through external circumstances; that is to say, may become weakened so that they either lose entirely the power to produce processes of disease in the organism, or at least can only cause mild forms of disease. This peculiarity is not alone of theoretical interest, but is also of high practical interest. It explains, on the one hand, to a certain extent, why a certain infection does not always run the same course, and, moreover, why alongside of severe attacks light ones also occur. On the other hand, it affords us the possibility of obtaining *material for inoculation* from attenuated cultures of bacteria, by means of which slight degrees of infection and also slight degrees of intoxication can be produced, which protect the organism from severe infection or cure an infection that has already taken place (cf. § 29).

Attenuation of the pathogenic properties of a fission-fungus can be effected by allowing higher temperatures, oxygen or light, or chemical antiseptic substances to act in a suitable manner upon the cultures as well as by cultivating the fungus in the body of animals possessing little susceptibility. In some forms, as in the diplococcus of pneumonia, it is only necessary to cultivate the bacteria in question upon artificial media to bring about attenuation; in others, such as the bacillus of chicken-cholera, prolonged exposure of the culture to the air suffices to bring about an attenuation. If it is desired to preserve the virulence of the pneumococci for a long time, it is necessary, from time to time, to inoculate the bacteria cultivated upon artificial media into rabbits, which are very susceptible animals. The glanders-bacilli and tubercle-bacilli and cholera-spirilla lose virulence if cultivated for a long time uninterruptedly upon artificial nutrient media. The streptococcus of erysipelas becomes so attenuated by continued cultivation in bouillon or nutrient jelly that it is no longer capable of killing even mice (Emmerich).

According to the investigations of Pasteur and of Koch, the virulence of anthrax-bacilli may be so attenuated by cultivation at 43° C. for about six days, or at 42° C. for about thirty days, that guinea-pigs are no longer killed by the inoculation.

A considerable attenuation of the anthrax-bacillus is obtained even by 10 minutes' heating at 55° C. (Toussaint), or by heating at 52° C. for 15 minutes, or at 50° C. for 20 minutes (Chauveau); moreover, the same result is also obtained by the action of oxygen at high pressure (Chauveau). The bacilli weakened by the influence of high temperature for a short time, regain their virulence very quickly by recultivation; the bacilli, on the contrary, which have been weakened at lower temperatures, remain attenuated through numerous generations. Spores of the bacillus of blackleg are rendered harmless by a temperature of 85° C. in six hours (Arloing, Thomas, Cornevin) without suffering any diminution in their power of reproduction. Moreover, the bacilli can be weakened without killing them by weak solutions of sublimate, thymol, eucalyptus-oil, nitrate of silver, etc.

The addition of carbolic acid in the proportion of 1 : 600 to the culture-fluid permits of the development of anthrax-bacilli, but destroys their virulence in twenty-nine days (Chamberland, Roux). In the same way attenuation is obtained by addition of bichromate of potash (from 1 : 2000 to 1 : 5000). Carbolic acid added in the proportion of 1 : 800 prevents at the same time the formation of spores.

The poison of rabies, which kills rabbits in a short time on inoculation, may be attenuated by drying at temperatures of 22–26° C. (Pasteur). According to Protopopoff, it is mainly the higher temperature which produces the attenuation.

If the bacilli of swine-erysipelas (Pasteur) are inoculated continuously into pigeons the virulence is so increased that not only pigeons die more quickly from the inoculation than at the beginning, but also hogs. But when, on the contrary, the swine-erysipelas bacilli are inoculated from rabbit to rabbit, they increase in virulence for rabbits, it is true, but lose in toxic power for swine.

It is possible to make hypotheses only in regard to the explanation of the nature of the attenuation of virulence of the bacteria by the methods above mentioned. If the bacteria cultivated for a long time upon artificial media change in virulence, perhaps this can be partially explained by assuming that in a series of generations the less virulent varieties, which certainly must often appear, gradually win the superiority. In the attenuation of virulence by heat, chemical reagents, etc., however, this explanation is not permissible. In this case it turns very likely upon a general weakening, a degeneration of the protoplasm. This assumption is in accord with the fact that such bacteria show a diminution in energy of growth (Flügge).

3. *General Considerations in Regard to the Examination of Fission-fungi.*

§ 166. If bacteria are suspected in any tissue-fluid or in the parenchyma it is first sought to discover them by microscopic examination. Occasionally this succeeds merely by looking at a drop of the fluid or of a smear-preparation of the tissue-juice diluted with salt-solution or distilled water. In other cases it is necessary to apply coloring. In this case the fluid above mentioned is smeared on a cover-glass and allowed to dry. In order to fix the dried substance the cover-glass is then heated over a flame, allowed to cool, and stained. For this purpose methylene blue is used by preference, the solution consisting of a 1 per cent. solution of the dye in a 1 : 10,000 solution of caustic potash. Aqueous solutions of fuchsin and methyl violet are also frequently used. For many bacteria special methods are also in use. In these methods the preparations are strongly overstained with a solution of gentian violet, or aniline-water fuchsin, or aqueous methyl violet, and the color subsequently removed with weak acids or with iodine and alcohol (Gram's method). In this way it is often brought about that only the bacteria remain stained, sometimes even certain bacteria only.

If it is desired to show the presence of bacteria in tissues, the latter are cut in small pieces, hardened in absolute alcohol, then cut in thinnest possible sections, and stained by appropriate methods. Here again the staining, as above mentioned, with gentian violet, methyl violet, and fuchsin is especially often employed. Good object-glasses are necessary for the microscopic examination; if possible, oil-immersion lenses and illumination with substage condenser are to be employed.

If it has been possible to demonstrate the presence of bacteria in the tissues in any way, the attempt is next made to cultivate them. For this purpose the methods developed by Koch are generally employed. These, in principle, consist in distributing the fluid containing the bacteria uniformly in a solution of gelatin or agar previously warmed, and pouring out some of the mixture upon horizontal glass plates. The fluid containing the bacteria is obtained either by scraping the tissue or by rubbing up pieces of tissue in sterilized salt-solution. The gelatin- and agar-solutions are liquid at higher temperatures and solid at lower. When the solutions become solidified the individual bacteria or spores become developed at points separated from one another.

By a proper application of the method varied colonies are subsequently obtained in the layer of gelatin spread out on the plate (Fig. 323). The colonies often differ from one another in appearance, even when examined with the naked eye. If the colonies are sufficiently separated from one another a small amount is to be taken from the individual colonies by means of a fine platinum needle, and transferred to a boiled potato (Plate I., Figs. 5 and 6), or to a gelatin plate free from bacteria, or upon the surface of the solidified nutrient fluid in a test-tube (Plate I., Fig. 4). Very often the infected needle is stuck into the solidified transparent medium contained in a test-tube (Plate I., Figs. 1–3).

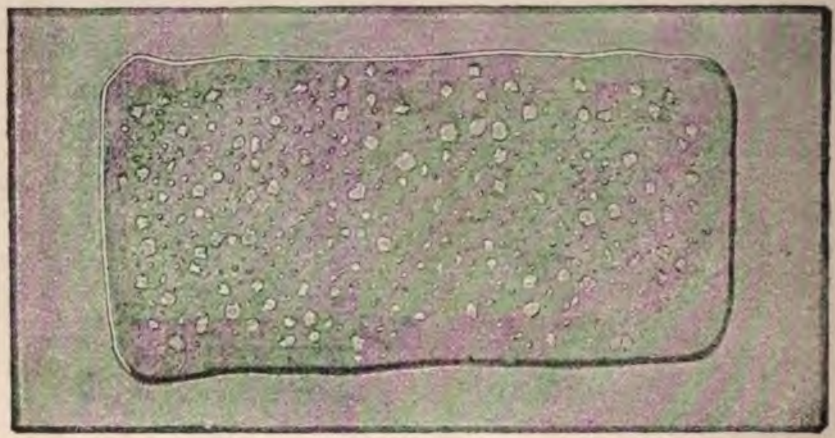
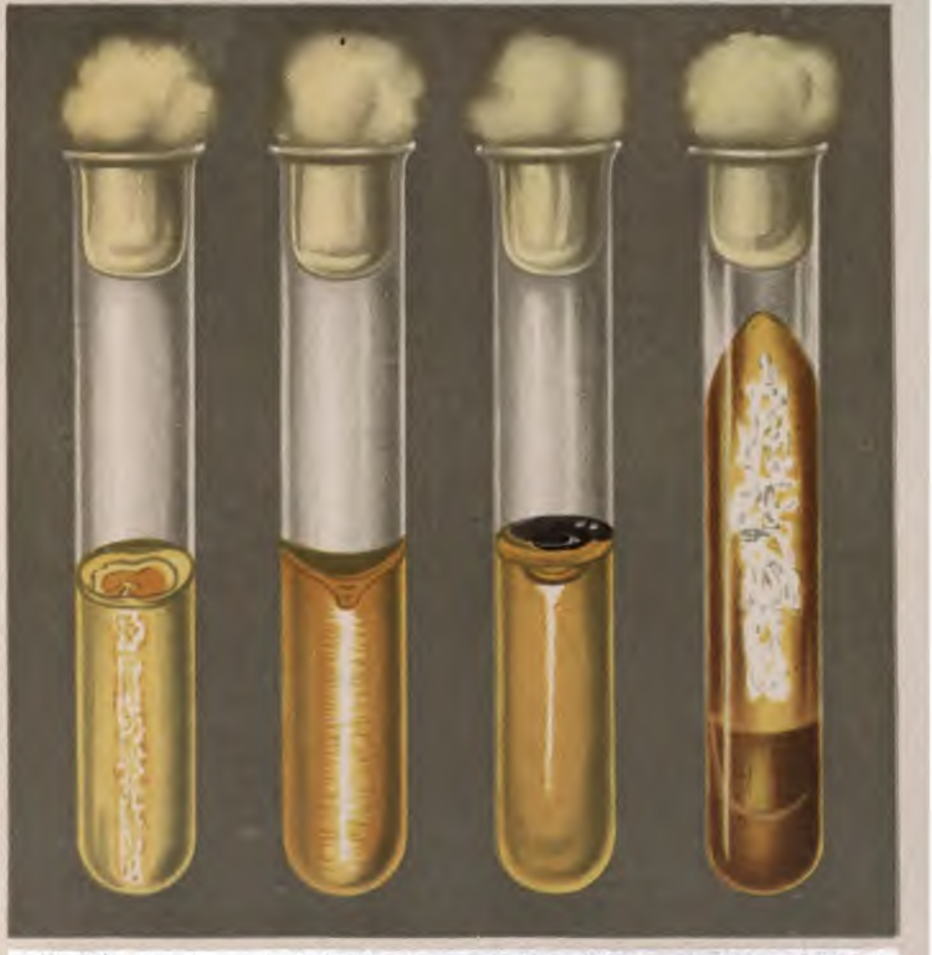


FIG. 323.—Gelatin plate containing colonies of small bacilli. These colonies are pellicle-like, with somewhat sinuous margins. Also small, round white colonies of cocci are present. Obtained from the exudate of a purulent peritonitis. (Diminished by one third.)

If the culture on the gelatin plate is pure, and the whole procedure is carried out with the necessary care and avoidance of contamination, pure cultures are obtained by the above method. In stab-cultures (Plate I, Figs. 1–3) as well as in smear-cultures on potatoes (Figs. 5 and 6) and on any other nutrient medium (Fig. 4), often special peculiarities show themselves which make it possible for the practised observer to recognize the form of bacteria. Still it will occasionally happen that a thorough microscopic examination of the colonies will also have to be made.

It goes without saying that all the above manipulations must be carried out with care, and that care must be had for the absolute cleanliness of the instruments that come into use—of the glass plates and test-tubes,—and that the nutrient media must be free from bacteria. Suitable procedures are easiest learned in laboratories specially arranged for the purpose. The long-continued heating of the instruments used or their subjection to high temperatures plays an important rôle. The necessary guidance is furnished in the various books on bacteriological methods of examination which have appeared recently.

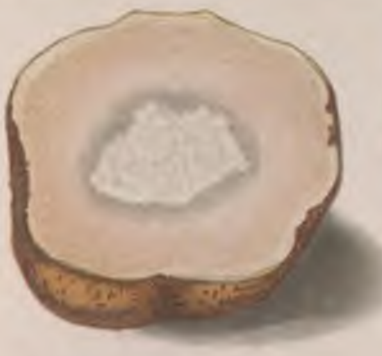


1. Stab-culture of **Staphylococcus Pyogenes Aureus** in Agar-Agar.

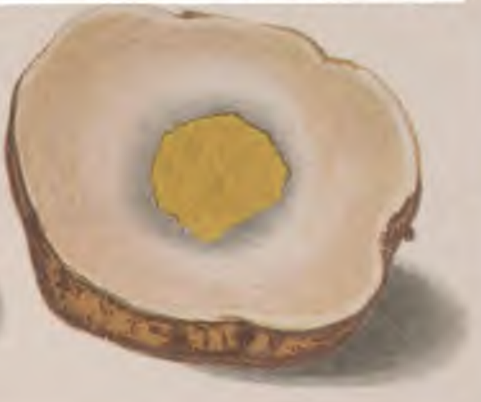
2. Stab-culture of **Bacilli of Swine Erysipelas** in gelatine.

3. Stab-culture of **Cholera Spirilla** in gelatine.

4. Culture of **Tubercle Bacilli** upon coagulated blood-serum (after Koch).



5. Culture of **Anthrax Bacilli** upon a boiled potato.



6. Culture of **Staphylococcus Pyogenes Citreus** upon a boiled potato.

Infusion of meat containing peptone and gelatin is most usually employed for making plates. This consists of a watery infusion of chopped meat, to which a definite amount of peptone and salt is added. This is, moreover, neutralized with carbonate of soda, and enough gelatin added to give a solid consistence at ordinary temperatures. For stroke- and stab-cultures sometimes this same gelatin is used (Plate I., Figs. 2 and 3), sometimes a jelly made of a mixture of watery extract of meat, peptone, and agar-agar (Plate I., Fig. 1), sometimes blood-serum that has been brought to coagulation by warming (Fig. 4).

For stab-cultures the jelly is allowed to solidify with the test-tube in a perpendicular position (Fig. 3), for stroke-cultures in an oblique position (Fig. 4).

Sterilized bouillon is often used for cultures. The inoculated nutrient media are either kept at room-temperature or at higher temperatures of 30–40° C. in an incubating-oven. The latter, however, is only possible with agar-agar, blood-serum, and potatoes, as the gelatin that is used becomes fluid at the temperature of the incubating-oven.

It goes without saying that the process just briefly described can be modified according to the exigencies of the case. Thus, for example, in cases in which the bacteria grow only at high temperatures it is necessary to use agar-agar plates and to do away with gelatin. Occasionally small pieces of tissue are excised and introduced directly into the nutrient solution. If it be desired to examine the cultures directly under the microscope, hanging-drop cultures are made. For many bacteria—for example, for cholera-spirilla—the use of cultures in hanging drops is to be recommended. In this method a drop of sterilized bouillon hangs down from the under surface of a cover-glass and is inoculated from a previously purified culture of a fission-fungus. After this the cover-glass is laid over the excavation in a hollow-ground slide. If evaporation of the drop is avoided by closing off the external air from the cavity in the slide —which may be effected by sticking on the cover-glass with oil or vaseline—the multiplication of the bacteria can be directly observed for a long time.

If the bacteria are sought in water a small amount of the water is distributed in gelatin and plate-cultures are made. Earth may be rubbed up in sterilized salt-solution. Air is made to pass in definite amount through sterilized salt-solution, and the salt-solution infected in this way is then mixed with gelatin, and from this gelatin plates are made.

The culture of the bacteria on different media, accompanied by the microscopic examination of the different stages of development, serves for a more precise characterization, and at the same time, also, for the determination of the species of fission-fungus in question. After its peculiarities have been sufficiently studied in this way its development in the animal body is tested. As experimental animals those most usually employed are rabbits, dogs, guinea-pigs, rats, mice, and small birds. Bacteria to be tested are introduced sometimes under the skin, sometimes directly into the blood-current, sometimes by inoculation into the inner organs, sometimes by inhalation into the lungs, sometimes by administration with the food into the intestinal tract. The fungus can be regarded as pathogenic for the animal in question if it multiplies in the tissues of the latter and produces morbid conditions. If relatively large amounts are inoculated the experimental animal may, under certain conditions, die, even if the bacteria do not increase at all in its body; for the poisonous substances ready-formed in the culture and introduced by inoculation often suffice to kill the animal.

Experience has taught that only some of the bacterial infections which occur in man, if transmitted to animals by inoculation, run the same course as in man; that is to say, only those which also occur otherwise in animals. In other cases the pathogenic fission-fungi which occur in man or certain animals are, it is true, pathogenic for the experimental animals, but the morbid process shows a different localization and a different course. In still a third case the experimental animals are partially or completely immune.

Inversely, fission-fungi that are extremely pathogenic for the experimental animals are often innocuous for other animals and for man.

II. The Different Forms of Fission-fungi and the Infectious Diseases Caused by Them.

1. *The Cocci and the Morbid Processes Caused by Them.*

(*a*) *Forms of Growth of the Cocci.—Saprophytic Cocci.*

§ 167. The **cocci** or *coccacei* (Zopf) are bacteria that always occur exclusively in the form of round or oval or lancet-shaped cells, and under no condition form rods. In their multiplication by division they often form aggregations of cells hanging together, and it is customary to designate these by special names, according to the character of the different forms that appear. Since certain forms of cocci are specially apt to develop in definitely shaped aggregations, many authors have found occasion to make different species and subspecies accordingly.

Many of the cocci multiply by transverse division of the spherical cell after it has become somewhat elongated. If in this case the spheres resulting by division remain together for some time in the form of double spheres, and if this form appears with especial frequency, they are called **diplococci** (Fig. 324, *b*). If rows of cocci in a plane result from the con-

Fig. 324.

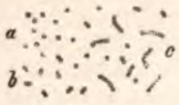


Fig. 325.

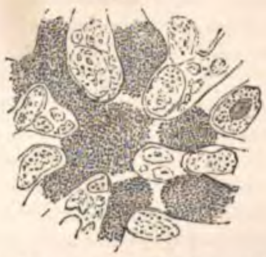


Fig. 326.

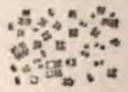


Fig. 327.

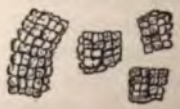


FIG. 324.—Streptococcus from a purulent peritoneal exudate of puerperal peritonitis. *a*, Separate cocci; *b*, Diplococci; *c*, Streptococci. (Magnified 500 diameters.)

FIG. 325.—Micrococcus colonies in a blood-capillary of the liver, as the cause of metastatic abscess-formation in pyæmic infection. Necrosis of the liver-cells. (Magnified 400 diameters.)

FIG. 326.—Cocci grouped in tetrads (merismopedia), from a softening infarction of the lung. (Magnified 500 diameters.)

FIG. 327.—Sarcina ventriculi. (Magnifi

tinuous division of the cells they are called **streptococci** (Fig. 324, *e*) or *torula-chains*. Masses of cocci united into a regular granular colony, and held together by a gelatinous substance which is derived from the membrane of the cocci, are called *zoöglœa*, and the cocci which often appear in this form, **micrococci** (Zopf) or *heaped cocci* (Fig. 325). For some of the forms belonging here the name **staphylococci** (Ogston and Rosenbach) or *grape-cocci* has come into use. Forms which, on the nutrient material, make round masses—recognizable as such even to the naked eye—and which contain, in a thick, gelatinous, cartilage-like membrane, one or more closely packed coccus colonies, are called **ascococci.**

Zopf introduced the name **merismopedia,** or *tablet-cocci*, for cocci which remain for a long time united in a four-celled tablet (Fig. 326). Others regard such bacteria as micrococci. The cocci that go by the name **sarcinæ** are characterized by dividing in three directions of space, so that compound cubical packets (Fig. 327) of round cells are formed from tetrads.

The names given above, which are used, as has been said, to designate different species, have only a limited value, and only to this extent: they represent the appearance corresponding to the forms of growth which characterize various kinds of cocci that differ very greatly from one another in their cultures as well as in their physiological properties. Still they are expedient for understanding quickly the manner in which a form of bacterium appears in any nutrient medium, such as a human being. The term micrococcus, moreover, is used by most authors for all the different cocci, and is not restricted to the staphylococcus.

The cocci not infrequently show a tremulous molecular motion in fluids. Independent motion has not been observed with certainty. Spore-formation has not been observed in most of them. According to Cienkowski, van Tieghem, and Zopf, the *Coccus mesenterioides*, leuconostoc, that makes a frog-spawn-like coating on sugar or parsnips, forms arthrogenic spores. When this is about to occur some particular cell in a torula-chain becomes somewhat larger and glistening. According to Prazmowsky, *Micrococcus ureæ* also forms spores.

The **saprophytic cocci** grow upon very different nutrient substrata, and cause by their growth in suitable media various processes of decomposition. Many of them also produce pigment. *Micrococcus ureæ* (Pasteur, van Tieghem, Leube) causes fermentative processes in urine, and in consequence of these carbonate of ammonia is formed out of urea. *Micrococcus viscosus* is the cause of the slimy fermentation of wine. The cause of the *glow seen in foul meat* was found by Pflüger to be due to a micrococcus that forms slimy coatings on the surface of the meat.

Among the pigment-producers the best known are the *Micrococcus luteus*, the *Micrococcus aurantiacus*, the *Sarcina lutea*, the *Micrococcus cyaneus*, and the *Micrococcus violaceus*, which produce yellow, blue, and violet pigment respectively when grown on boiled eggs or potatoes.

Saprophytic cocci are found as well in the cavity of the mouth and in the intestines as on the surface of the skin, and occur occasionally, also, in the lungs. *Micrococcus hæmatodes* (Babes) is said to be the cause of red sweat, and produces red-colored zoöglœa masses.

Sarcina ventriculi (Fig. 327) occurs not infrequently in the stomach of man and animals, especially when abnormal fermentations are going According to Falkenheim, the stomach sarcina can be cultivated atin, forming round yellow colonies which show colorless spherical monococci, diplococci, and tetrads, but never contain cubical packets. They form these, however, in neutralized hay-infusion, and their growth causes the souring of the infusion. The membrane of the sarcina is said to consist of cellulose.

Micrococcus tetragenus (*merismopedia*) is often found in human sputum and consequently also in the mouth and throat; it is also found in the walls of tuberculous cavities or in hæmorrhagic softening foci in the lungs, and forms tetrads in multiplying, the cells of which are held together by a slimy membrane. On gelatin it forms round or oval lemon-yellow colonies. It is pathogenic for white mice, developing in their blood. Gray house-mice are almost immune.

Micrococcus fœtidus is described by Rosenbach as having been found in carious teeth. In the intestinal tract Brieger and Escherich have found cocci. In the cavity of the mouth cocci are always to be found along with bacilli.

(*b*) *Pathogenic Cocci.*

§ 168. The **pathogenic cocci** cause mostly diseases which run an acute course in human beings and in animals, and at present there are already quite a number that are well known and have had their action upon tissues studied. They are able to act deleteriously upon the tissues and to excite inflammation in them mainly by the *excretion of certain poisonous substances* (*toxins* or *toxalbumins*).

In the first place there is a group of cocci which occur especially in suppurative processes, and are, moreover, the cause of the suppuration; they may therefore be called **pus-cocci.** A given suppurating focus contains sometimes only one single form of coccus, sometimes two or more of them.

One which occurs oftenest is the **staphylococcus pyogenes aureus** (Ogston, Rosenbach, Krause, Passet). This coccus tends to form cloudy or aggregated or grape-shaped colonies in animal tissues (Fig. 325, Fig. 328, *c*, c_1, and Fig. 329, *d*), or it may form swarms; but it not infrequently forms diplococci and tablet-cocci, and torula-chains. It can be stained with different aniline dyes, and retains the stain by Gram's method. It grows on gelatin, agar-agar, and potatoes even at room-temperature, and forms whitish colonies that afterward turn golden yellow on places exposed to the air (Plate I., Fig. 1). The gelatin around the colonies becomes slowly liquefied. By inoculation of pure cultures suppuration can be produced in mice, rabbits, and guinea-pigs. In man the presence of large quantities of staphylococci (Fig. 328, *c*, c_1, and Fig. 329, *d*) causes necrosis of tissue (Fig. 325 and Fig. 328, *b*), and subsequently inflammation (Fig. 328, *d*, *e*) and suppuration (Fig. 329, *e*, *f*), which finally run on to abscess-formation (Fig. 329, *g*). In the skin it can cause those forms of inflammation which are termed *acne*, *eczema*, *furuncle*, and *cutaneous* and *subcutaneous abscesses*, which are all characterized by suppuration and destruction of tissue. It can penetrate into the cutaneous and subcutaneous tissues through wounds, as well as by way of the hair-follicles or the ducts of the cutaneous glands. In the interior of the body it can cause suppuration of the various tissues. It has been observed frequently in *suppuration of the bones and joints* (*osteomyelitis* and *periostitis infectiosa*), as well as in *purulent inflammation of the lung, liver* (Fig. 328), *pleura, peritoneum, muscle, endocardium, myocardium, kidney*, etc. Ac-

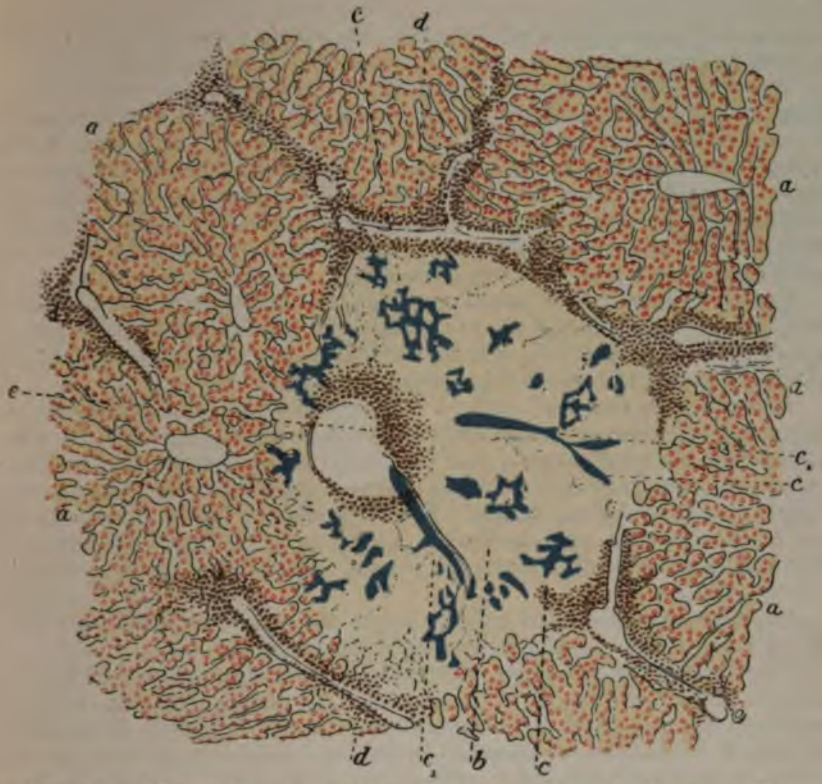


FIG. 328.—Metastatic aggregation of micrococci in the liver. *a*, Normal lobule; *b*, Necrotic lobule; *c*, *c₁*, Capillaries and veins filled with micrococci; *d*, Periportal small-cell infiltration; *e*, A collection of small round cells partly inside, partly outside a vein into which a venula centralis filled with micrococci opens. (Preparation stained by Gram's method with gentian violet and with vesuvin, and mounted in Canada balsam. Magnified 40 diameters.)

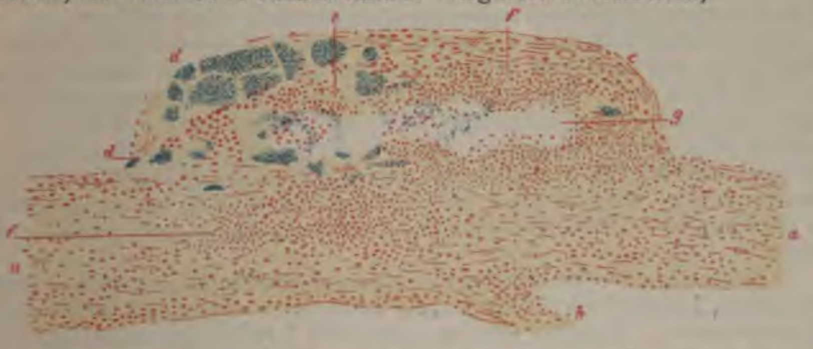


FIG. 329.—Endocarditis pustulosa caused by *Staphylococcus pyogenes aureus*. *a*, Tissue of the posterior segment of the mitral valve; *b*, Threads of tendon; *c*, Pustular protuberance of the upper surface of the mitral valve; *d*, *Staphylococcus pyogenes aureus*; *e*, Staphylococci intermixed with pus-corpuscles; *f*, Pus-corpuscles with cocci; *g*, Small abscess. (Preparation hardened in alcohol, treated by Gram's method and subsequently stained with vesuvin, and mounted in Canada balsam. Magnified 60 diameters.)

cording to investigations of Ullmann, the staphylococcus is very often present in large numbers in the air, especially of rooms much used.

In many cases, as can be proved, it gets into the inside of the tissues through wounds, and is taken up by the lymph-vessels and veins in whose neighborhood and in whose walls it has settled, and then is conveyed farther by the blood-current. The suppurations in the internal organs bear, therefore, the character of *metastatic processes*, and the term *pyæmia following infection of wounds* is applied to them. In other cases the infection starts from the air-passages or from the intestinal tract, especially where ulcers furnish a portal of entrance.

In still other cases the portal of entrance cannot be made out. This is true, for example, in many cases of endocarditis and myocarditis, suppurative or septic osteomyelitis and periostitis, suppurative pleuritis, etc., in which the process is one of *cryptogenetic infection*.

According to the observations referred to above, the *Staphylococcus pyogenes aureus* causes mostly circumscribed suppurations; still its virulence is not always the same, and hence the multiplication of these bacteria in the tissues does not always lead to suppuration, but often merely to *light transitory inflammations*. In course of time the cocci usually die out, after which the process heals. Under certain circumstances, however, they seem able to remain for a long time—weeks or even months—in the tissues.

Staphylococcus aureus is able to cause the suppurations above mentioned as well alone as in company with other cocci.

Staphylococcus pyogenes albus (Rosenbach) corresponds under the microscope with the staphylococcus just described, but appears white in cultures. Its action upon the human and animal organisms is the same as that of *Staphylococcus pyogenes aureus*, and is observed alone as well as in company with the latter in foci of suppuration.

Staphylococcus pyogenes citreus (Passet) is also a pus-producing fission-fungus; it occurs, however, more seldom than the first two. It forms citron-yellow colonies (Plate I., Fig. 6).

Micrococcus pyogenes tenuis, a coccus first observed by Rosenbach in abscesses, is somewhat larger than staphylococcus, and forms cultures almost as clear as glass on agar-agar. It seems to occur seldom.

Streptococcus pyogenes (Ogston, Rosenbach, Krause, Passet) is characterized by a tendency to form chains of from four to ten links or more, and also diplococci. The individual cocci are somewhat larger than the cells of the yellow staphylococcus. Staining succeeds very well by Gram's method (Fig. 330). On gelatin plates it forms only very small, slightly elevated colonies that grow slowly, appearing yellow or brownish under the microscope. On agar-agar the colonies are cloudy and not transparent. In gelatin stab-cultures it forms small whitish, almost transparent colonies.

It produces, on subcutaneous inoculation into animals, sometimes only transitory, insignificant inflammation (rabbits), sometimes a small area of suppuration. Healthy rabbits bear even intravenous injection. If the valves of the heart are previously injured it is possible sometimes to produce endocarditis (Flügge, Wyssokowitsch).

The streptococcus is often observed in human beings, and causes suppuration and sero-purulent and fibrinous exudates which have the tendency to spread over large areas, so that wide-spread cloudy, purulent, gelatinous infiltrations, *phlegmonous inflammations*, and *purulent œdema* result. It can penetrate from wounds or from the puerperal uterus into the tissues; but such inflammations can also occur, *without any observable changes at the portal of entrance*, in subcutaneous, intermuscular, mediastinal, peripharyngeal tissues, in the serous and mucous membranes or the submucosa of the nose and its adjoining cavities, in the submucosa of the stomach, etc.

The streptococci lie in the foci of inflammation partly free in the tissues (Fig. 331) and partly in the cells (Fig. 330, *b*). The former is especially observable where the cocci penetrate into the tissues (Fig. 331, *a*). In the region of the coccus invasion the tissues in time succumb to necrosis (*c*), and finally are destroyed, becoming disintegrated and liquefied.

If a tissue becomes the seat of suppuration, out of such foci the products caused by the process of decomposition are taken up by the juices of the body, and often lead to morbid conditions of the entire organism. Cocci themselves often get into the circulation and transfer the process to other organs.

If the infection of a wound leads to a metastatic or embolic inflammation and suppuration accompanied by fever, the process is called **pyæmia.** If a general disease with severe symptoms on the part of the nervous system appears, with disturbance of the regulation of temperature and blood-circulation, often accompanied, also, by diarrhœa, etc., without the formation of metastases, the disease is classed as **septicæmia** or **septhæmia.**

Both terms are collective, since a metastatic inflammation accompanied by fever is not necessarily brought about by one single form of bacterial infection, and the manifestations of septicæmia are not always caused by the same noxious agent.

The essence of septicæmia is a poisoning of the organism by toxins, toxalbumins, ferments, and other products of bacterial decomposition—i.e., it is a septic intoxication. As these products differ according to the stage of the putrefaction as well as according to the nature of the putrefactive agent, it follows that the intoxication cannot always be caused by the same substance. Simultaneously with the intoxication, *infection of the blood with micro-organisms* can also take place; but this is not necessary, and it is possible to distinguish between a *septic intoxication* pure and simple, on the one hand, and a *bacterial septicæmia*, on the other. Moreover, the manifestations of *septicæmia* may be combined *with pyæmic inflammation*, a combination that has given rise to a disease that has been designated **septicopyæmia** or **pyosepthæmia.**

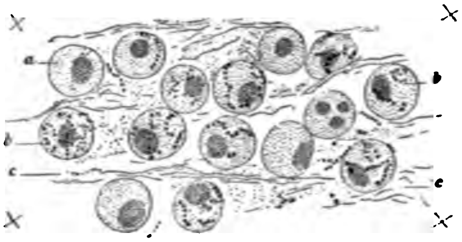


FIG. 330.—*Streptococcus pyogenes* from a phlegmonous inflammatory focus of the stomach. *a*, Leucocytes; *b*, Leucocytes with streptococci inside; *c*, Free streptococci. (Preparation hardened in alcohol, stained by Gram's method, and mounted in Canada balsam. Magnified 500 diameters.)

Septic blood-poisonings follow most frequently from wounds and from foci of suppuration situated in the parenchyma of the tissues, but the putrid substance producing the intoxication may be taken up from the intestines or the lungs. The anatomical changes in the infected wounds are often insignificant and scarcely recognizable.

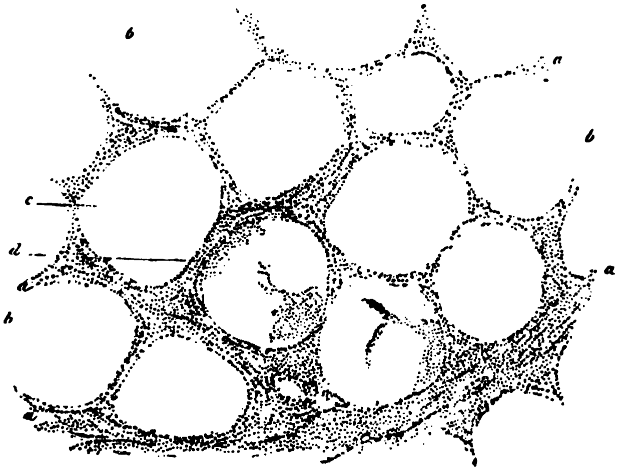


FIG. 331.—Pectoral muscle beset with large numbers of the *Streptococcus pyogenes*, from a case of phlegmonous inflammation of the subcutaneous and intermuscular connective tissue, due to cadaveric poisoning. (The phlegmon of the wall of the chest developed two days after the finger was injured, and the intermediate lymph-vessels of the arm showed no evidences of being involved.) *a*, Perimysium internum full of streptococci; *b*, Transversely cut muscular fibres. still intact; *c*, Transversely cut muscular fibres which are beginning to degenerate; *d*, Muscular fibres into which the cocci have penetrated. (Preparation treated with gentian violet and vesuvin, and mounted in Canada balsam. Magnified 350 diameters.)

If the first inflammatory processes start in the depth of the body they are characterized as **cryptogenetic pyæmia** and **septicopyæmia**. The bacteria producing them get into the tissues from the intestinal canal or the lung, or from the skin, or from any small wound, and are thence conveyed with the blood-current or the juices to any particular place without leaving behind any demonstrable change.

As is seen from the foregoing, **suppurative processes** may be produced in man as well as in animals by different bacteria, and not infrequently many forms of bacteria are contained simultaneously in a focus of suppuration. Besides the pus-cocci proper, the gonococcus, the *Diplococcus pneumoniæ*, the *Bacillus typhi abdominalis*, the actinomyces, and the glanders-bacillus can also produce suppuration. According to Flügge, the streptococci which occur in suppuration do not all belong to the same species. Thus Flügge found a streptococcus in a necrotic focus in a leucæmic spleen (*Streptococcus pyogenes malignus*) that closely resembles the ordinary *Streptococcus pyogenes* under the microscope and in cultures, but kills mice and rabbits in a few days when introduced by subcutaneous inoculation; at the same time producing not only local inflammation at the point of inoculation, but also metastatic inflammation, and appearing as well in the blood.

Different authors have used the term *septicæmia* also for *bacterial infections of the blood* which can be produced experimentally by inoculation of animals, and which are characterized by the fact that *the bacteria multiply in the blood*. It would be more proper to apply the term *bacteriæmia* to such processes.

§ 169. **Streptococcus erysipelatis** is the cause of the inflammation of the skin and mucous membranes called *erysipelas*. According to Fehleisen, it may be cultivated upon the meat-infusion-peptone-and-gelatin mixture; and the cocci from cultures produce typical erysipelas when inoculated into human beings. The fission-fungus of this disease, moreover, may be inoculated into rabbits (Ziegler, Fehleisen), and produces an inflammation radiating from the point of inoculation. It is killed in one minute by 3 per cent. solutions of carbolic acid or by a 1 : 1000 corrosive-sublimate solution (Fehleisen).

The cocci get into the skin through small wounds, and thence into the lymph-vessels (Fig. 332, *a*, *b*), but occasionally also into the blood-current.

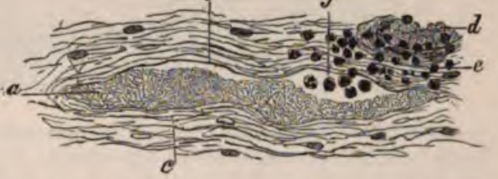


FIG. 332.—Colonies of *Streptococcus erysipelatis*: *a*, in a lymph-vessel, *b*, in part composed of thickly packed spheres, in part of torula-chains; *c*, Neighborhood of the lymph-vessel, with pale unstainable nuclei; *d*, Vein; *e*, Perivenous cellular infiltration of tissue; *f*, Accumulation of cells in the lymph-vessel. (Section of rabbit's ear two days after inoculation with erysipelas-cocci, treated with gentian violet, and mounted in Canada balsam. Magnified 250 diameters.)

Observed in living beings, erysipelas runs its course in the form of a reddening and swelling of the skin extending at the periphery and accompanied by a febrile condition. In some cases vesicles are formed in the skin, and under certain circumstances individual portions of the skin become even gangrenous.

The cocci that spread in the lymph-vessels form first torula-chains (Fig. 332, *a*) and afterward colonies that fill the lymph-vessels more or less fully (Fig. 332, *b*, and Fig. 333, *h*, *i*) and not infrequently spread over the contiguous connective tissue (Fig. 333, *k*).

In the area of a larger bacterial invasion and in its neighborhood the tissue usually degenerates and often becomes devoid of nuclei—necrotic (Fig. 332, *c*, and Fig. 333, l, l_1). At the same time an inflammation occurs in the neighborhood which is connected directly or indirectly with the tissue-lesion caused by the bacteria. Consequently it either represents a reaction dependent upon the degeneration of tissue, or is to be regarded as an alteration of the vessel-walls by the products formed by the bacteria. It leads to a dense cellular infiltration of the tissue (Fig. 332, *e*, and Fig. 333, m, m_1). A liquefaction of the cells can take place in the epithelium (Fig. 333, e, f, g, g_1) under certain conditions, and this results in the formation of vesicles. In the region of cellular infiltration the cocci lie mostly between the cells, here and there also in the cells. As long as the process spreads the cocci lie most abundantly in the periphery of the region occupied (Fig. 332, *a*). Next to it, toward the centre, comes the area of cellular infiltration which corresponds to the external zone of redness. With the appearance of the healing process the bacteria vanish, but it is impossible to determine from an anatomical examination why a further spread ceases. Since the inflammatory accumulation of leucocytes offers no resistance to the spread of bacteria, but, on the contrary, may be said

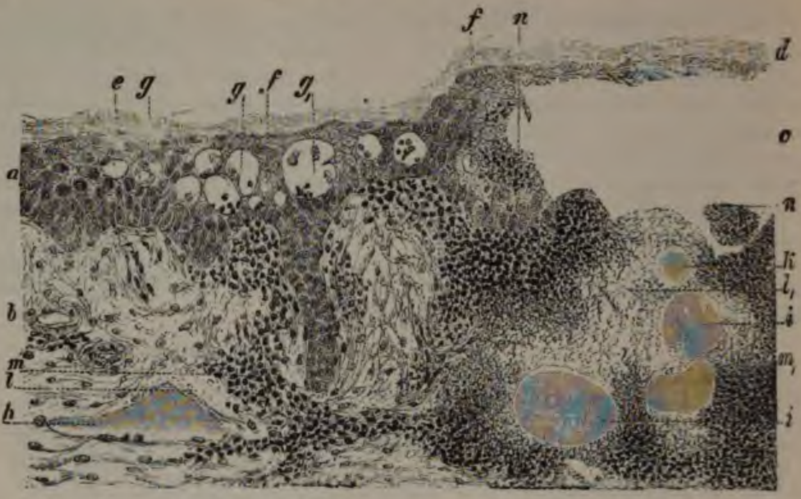


FIG. 333.—Section of the skin from a case of erysipelas bullosum. *a*, Epidermis; *b*, Corium; *c*, Bladder-like cavity; *d*, Cover of this cavity; *e*, Epithelial cell with vacuole; *f*, Swollen cell with swollen nucleus; *g*, g_1, Cavity caused by the melting down of epithelial cells, and containing fragments of the same and pus-corpuscles; *h*, Lymph-vessel partially filled with streptococci; *i*, Lymph-vessels completely filled with streptococci; *k*, Colony of streptococci located in the midst of the tissues; *l*, l_1, Necrotic tissue; *m*, Cellular, m_1, fibrinocellular infiltration of the tissues; *n*, Fibrinocellular exudation in the bladder-like cavity. (Preparation stained with alum carmine and mounted in Canada balsam. Magnified 60 diameters.)

rather to limp after it, the destruction of the bacteria cannot be due to this cause. Very likely the growth of the bacteria is hemmed by chemical substances. Metastases may form by an eruption of the bacteria into the blood-current.

The *Streptococcus pyogenes* is very much like the streptococcus of erysipelas; many assume that it is identical with the latter (von Eiselsberg, Jordan, Fränkel).

§ 170. **Micrococcus gonorrhœæ,** *sive* **gonococcus** (Fig. 334), is a coccus first described by Neisser in 1879. It is constantly present in the purulent catarrh, called gonorrhœa, of the male and female urethra and the female genital canal (especially that of the uterus), as well as in the secretion of blennorrhœa of the eye, and it is also regarded as the cause of the gonorrhœa and of the blennorrhœa of the eye. Besides the specific cocci, other cocci may also be present in the gonorrhœal secretion, some of them resembling the specific cocci very closely. The secretion may, moreover, also contain the pus-cocci.

According to Oppenheimer and Bumm, it can be cultivated upon coagulated human blood-serum; according to Leistikow and Löffler, also upon blood-serum-gelatin mixture; according to Wertheim, upon human blood-serum-agar mixture; according to Finger, Ghon, and Schlagenhaufer, upon urine-agar mixture. It makes a thin, smooth, grayish-yellow coating upon the surface of the nutrient medium, but dies out very easily and grows only at higher temperatures.

Animals enjoy immunity from infection by inoculation. Efforts were made by Bockhart and Bumm to inoculate human beings with gonococci cultivated on artificial media, and they obtained in this way a purulent catarrh of the inoculated mucous membrane. The experiments of Bumm, particularly upon two women, seem to have given a positive result.

The coccus forms mostly clumps in the purulent secretion of the mucous membrane affected with gonorrhœa. It appears largely in the form of diplococci with the opposing surfaces flattened (Fig. 334), partly free (*a*) and partly inclosed in cells (*b*); it stains readily with aniline dyes, but becomes decolorized by Gram's method.

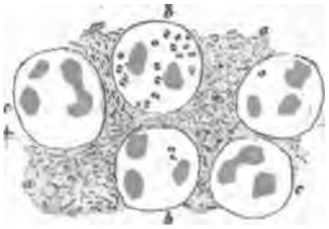
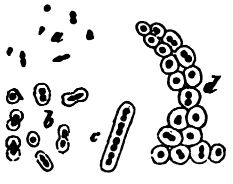


Fig. 334.—Gonococci in the secretion from the urethra in fresh gonorrhœa. Cover-glass preparation stained with methylene blue. *a*, Mucus with separate cocci and diplococci; *b*, Pus-cells with diplococci; *c*, Pus-cells without diplococci. (Magnified 700 diameters.)

According to Bumm, Gerheim, and Touton, the gonococcus penetrates into the mucous membrane and lies sometimes between and sometimes within the epithelial cells and leucocytes. Only the superficial layers of the connective tissue are penetrated. The extent to which the inflammations following gonorrhœa (peri-urethral abscesses, inflammations of the prostate gland, of the epididymis, of the seminal vesicles, of the bladder, of Bartholin's glands, of the tubes, of the ovary, of the pelvic peritoneum, and of the joints) are due to the spread of the gonococcus on the one hand, or to secondary infection with the pus-cocci on the other, is still a matter of dispute. From the investigations which have thus far been made it can no longer be doubted that the gonococcus may become widely spread over the mucous membranes. It has also been found repeatedly in inflamed Fallopian tubes, ovaries, and joints, in perimetritic and parametritic inflammatory foci and in peri-urethral abscesses, and is to be regarded as the cause of the inflammation. Still the processes leading to suppuration, and also the metastases in remote organs, seem to depend oftener upon the presence of pus-cocci.

A coccus is described as **trachoma coccus** which is regarded as the cause of *trachoma*, or *Egyptian ophthalmia*, or *conjunctivitis granulosa*—a well-known inflammation of the conjunctiva and of the cornea. According to Michel, it has a close resemblance to the gonococcus, but is smaller than the latter. It stains with all the basic aniline dyes, and the gentian-violet stain is retained by treatment according to Gram's method. It grows on nutrient gelatin as well as on coagulated blood-serum and agar-agar, best at the body-temperature, requires oxygen, and forms cultures at first white, afterward turning light yellow. Transferred to the connective tissue of the human eye, it is said to cause a granulating conjunctivitis, characterized by an extensive cellular infiltration, producing in the conjunctiva little nodules resembling lymph-follicles, which are called trachoma-nodules, long known in spontaneous trachoma.

§ 171. The **Diplococcus pneumoniæ** (Weichselbaum) is a coccus which was first thoroughly studied by Fränkel and by Weichselbaum. It occurs in the form of spherical, oval, or lancet-shaped cells (Fig. 335, *a*, *b*, *c*, *d*), in some instances naked (*a*), in others surrounded by a gelatinous cap-



sule; and it often forms either double cocci (*b*), or spheres in chains (*c*), or colonies spread out in a plane (*d*).

FIG. 335.—*Diplococcus pneumoniæ* of Weichselbaum and Fränkel. *a*, Cocci without a capsule; *b*, Single cocci and double cocci in a gelatinous envelope; *c*, Chain-cocci with a gelatinous envelope; *d*, Colonies of cocci. (Magnified 500 diameters.)

According to the observations of Fränkel, Weichselbaum, and others, it is the cause, in a large number of cases—according to Weichselbaum, 71 per cent.—of the lung-affection called *croupous pneumonia*, in which the lung is the seat of an acute inflammation which is ushered in by a congestive hyperæmia. In the course of the disease the alveoli over large areas become filled with a coagulated exudate which consists of desquamated epithelium, leucocytes, red blood-corpuscles, fluid, and fibrin, and which, under favorable conditions, becomes liquefied and absorbed. Numbers of observations have shown that it can cause inflammatory processes bearing the characteristics of catarrhal bronchopneumonia—processes, therefore, which encroach upon the lung-tissue by extension from the bronchi, and which are characterized by the appearance of an exudate partly serous, partly cellular. The cocci are found during the disease principally in the inflamed area of the lung, but they may also be met with in neighboring areas—in the pleura, and, under certain circumstances, in the pericardium, in the peritoneum, in the meninges (A. Fränkel, Foà, Bordoni-Uffreduzzi, Weichselbaum, Ortmann), in the cavities adjacent to the nose, in the cellular tissue of the neck, in the mediastinum, in the submucous tissue of the soft palate and throat, even in the conjunctiva (Weichselbaum); and in all of these localities they cause inflammatory changes. Occasionally they may be found in the juice of the spleen and in the blood, and are said to pass into the fœtus in pregnant women (Viti). They are therefore, under certain circumstances, widely distributed throughout the body. They may cause a serofibrinous inflammation in the meninges, the pleuræ, the pericardium, and the peritoneum, and under certain conditions they may also cause seropurulent and fibrinopurulent inflammation, without the appearance simultaneously of a pneumonia. They can, furthermore, cause inflammation of the endocardium, of the kidneys and of the joints (Samter), and are also found in abscesses (Haegler, Ortmann, Samter). In many cases the mouth and the nose and throat—where they are occasionally also found in healthy individuals (Weichselbaum, Fränkel)—seem to form the portal of entrance. Accordingly, in cerebral and cerebrospinal meningitis (Weichselbaum) the maxillary cavity, the tympanic cavity, and the cribriform labyrinth often contain exudate with diplococci. The diplococci are found in the exudate in all the forms which we have enumerated. The gelatinous capsule may show a very variable thickness.

In cover-glass preparations the cocci, as well as their capsule, stain well with fuchsin and gentian violet dissolved in aniline water. If the cocci stained with gentian violet are treated with a solution of iodine and alcohol they retain the stain. They will not grow on gelatin at ordinary room-temperature, but on slightly alkaline blood-serum gelatin and agar-agar kept at a temperature above 22° C., best at the temperature of the human body. They form delicate, translucent, glistening cultures which suggest the deposit of dew on a cover-glass (Fränkel) and consist of diplococci and chain-cocci without capsules. The growth is, however, scanty, and easily dies out. Cultures do not succeed on potatoes.

Inoculated upon rabbits, guinea-pigs, and mice, they multiply in the form of capsule-cocci, especially in the blood and in the serous cavities, and may also cause pneumonia with bloody serous exudate (Weichselbaum). Rabbits are specially sensitive, as they die in from thirty-six to forty-eight hours after subcutaneous inoculation, with symptoms of septicæmia. If pure cultures are injected into the pleural cavity of rabbits a pleurisy results, as well as a splenization of the lung in which the parenchyma is filled with a bloody serous exudate. The sputum of a pneumonia patient is pathogenic for rabbits, since it contains the cocci.

According to A. Fränkel, the cocci lose their poisonous properties very easily, especially if they are cultivated in milk; and if it is desired to retain the virulence they must be inoculated from time to time into susceptible animals. Cultivation of the cocci at 42° C. for one or two days destroys their virulence.

The *Diplococcus pneumoniæ* belongs to those bacteria whose *physiological characteristics are very variable.* Foà distinguishes, according to the principal places in which they are encountered, a *pneumococcus* and a *meningococcus.* Acccrding to Emmerich, in bouillon-cultures there is formed a sediment at the bottom containing some resistant forms which remain capable of development for months. Rabbits may be rendered completely immune (Emmerich) by repeated injections of much-diluted cultures (five thousand times diluted) of increasing virulence, so that 30 cc. of cultures of full virulence are borne without any striking disturbance. The injected bacteria are killed in the course of a few days. The serum of immunized rabbits can cure pneumococcus infection in rabbits and mice.

The *Diplococcus pneumoniæ*, it is true, is the most frequent, but not the only cause of croupous pneumonia. In a small percentage of cases a *streptococcus* occurs in pneumonic lungs that resembles very closely the *Streptococcus pyogenes*—possibly it is identical with it. Cases also occur in which the exudate contains the *Staphylococcus pyogenes aureus*, also the *albus*, sometimes alone, sometimes along with diplococci. Furthermore, a part of the cases are to be referred to the invasion of the *Bacillus pneumoniæ* of Friedländer (cf. § 178). Staphylococci and streptococci appear particularly in pneumonias occurring in the course of pyæmic infections. In the course of other infectious diseases, as, for example, typhoid fever, croupous pneumonia may be caused by the specific bacteria in question (typhoid-bacilli).

Bronchopneumonias—i.e., inflammations of the lungs arising from inflammations of the bronchi or from inspiration of inflammatory irritants from the air-passages—have a very varied etiology, and are partly attributable to the entrance of the *Diplococcus pneumoniæ* or of staphylococci and streptococci into the lungs, and partly to other specific infections the causes of which are unknown, as measles and whooping-cough; often also to mixed infection and to the inspiration of foul substances, etc.

Klebs, and subsequently Eberth and Koch, published papers upon the occurrence of cocci in croupous pneumonia. More thorough investigations, however, were first made by Friedländer, Frobenius, A. Fränkel, Weichselbaum, Talamon, Senger, Foà, Bordoni-Uffreduzzi, and others.

§ 172. The pathogenic significance of the bacteria above mentioned is proved by experiments upon animals; and although the biology of these bacteria, in some cases, is only incompletely known, still there is no question as to their etiological connection with the diseases concerned in the majority of cases.

In another category of infectious diseases cocci have been often observed and described, it is true, and also pronounced to be the cause; but at the present time there is nothing certainly known about them, and it is very likely that many of the bacteria found stand in no sort of relation to the diseases concerned, and constitute only secondary colonizations. To this category belong the cocci found in variola, varicella, scarlatina, morbilli, influenza, yellow fever, acute yellow atrophy of the liver, and mycosis fungoides.

Among the **infectious diseases occurring in animals** there are also a number supposed to be **caused by cocci**; thus the cattle-pest, the pleuropneumonia of cattle, the myofibroma of horses (Johne), and the pneumonia of horses (Perroncito).

Various affections can be produced experimentally in animals by the inoculation of cocci—e.g., the *Micrococcus tetragenus*, the staphylococci, streptococci, and the *Diplococcus pneumoniæ*.

Infectious Diseases of Animals said to be Caused by Cocci.

1. According to Poels and Nolen,[*] monococci and diplococci, some of them with a gelatinous capsule, are found constantly in the lungs and pleural exudate, in *contagious pleuropneumonia of cattle.* On gelatin and agar-agar they make mostly white colonies that later become cream-colored. Pure cultures injected into the lungs of rabbits, guinea-pigs, dogs, and cows cause pneumonic changes. Cornil and Babes found various bacteria in the exudate.

2. According to Semmer and Archangelski,[†] the microparasite of cattle-pest is a micrococcus. According to Metschnikoff and Gamaleia,[‡] it is a bacillus. The disease is anatomically distinguished by inflammation of the intestinal tract, bearing partly a croupous and diphtheritic character, as well as by swelling and sometimes even by necrosis of Peyer's plaques.

3. According to Schütz,[§] the *epidemic lung-disease of horses, infectious pneumonia,* is caused by an oval *coccus,* which is not identical with the *Diplococcus pneumoniæ* of Fränkel or the *Bacillus pneumoniæ* of Friedländer, and consequently not identical with the fission-fungus described by Perroncito[||] in the pneumonia of horses, and held to be identical with the *Diplococcus pneumoniæ.*

4. According to Schütz,[¶] Sand and Jensen,[**] and Poels,[††] the strangles of horses is an infectious disease in which the mucous membranes of the upper respiratory tract are the seat of a mucopurulent inflammation, in which, moreover, the lymph-glands pertaining to the part become swollen and some of them suppurate. It is caused by a *coccus in chains,* which may be cultivated and which produces strangles in horses on inoculation (Schütz).

5. According to Hess and Borgeaud,[‡‡] the infectious inflammation of the udder which is designated yellow *Galt,* and which occurs in cows, goats, and sheep, is caused by a streptococcus.

6. Babes found in hæmoglobinuria of cattle—a disease that occurs in epi-

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[*] *Fortschr. der Med.,* 1886.

[†] *Centralbl. f. d. med. Wiss.,* 1883, and *D. Zeitschr. f. Thiermed.,* xi.

[‡] *Centralbl. f. Bakt.,* i., 633.

[§] "Die Ursachen der Brustseuche des Pferdes," *Archiv f. wissensch. u. prakt. Thierheilk.,* 1887, and *Virch. Arch.,* 107. Bd., 1887.

[||] *Arch. ital. de biol.,* vii., 1886.

[¶] "Der Streptococcus der Druse der Pferde," *Arch. f. wissensch. u. prakt. Thierheilk.,* xiv., 1888, and *Zeitsch. f. Hygiene,* iii.

[**] "Die Aetiologie der Druse," *Deutsche Zeitsch. f. Thiermed.,* xiii.

[††] "Die Mikrokokken der Druse der Pferde," *Fortsch. d. Med.,* vi.

[‡‡] "Eine contagiöse Euterentzündung, gelber Galt genannt," *Schweizer Arch. f. Thierheilk.,* 30. Bd., 1888.

demics in Rumania—a coccus resembling the gonococcus, which he regards as the cause of the disease.[*]

7. According to Semmer, Friedberger, and Mathis,[†] the *distemper of dogs* is also caused by a coccus, which can be cultivated pure and which causes the distemper in dogs when it is inoculated subcutaneously.

8. *The foot-and-mouth disease of cattle*, according to Klein, is caused by a streptococcus[‡] which, on nutrient gelatin, blood-serum, and agar-agar-peptone bouillon, slowly develops colonies in the form of closely aggregated small points or drop-like spots. In recent years, Schottelius[§] and Kurth[‖] have also found a streptococcus in the organs of animals sick of the foot-and-mouth disease; but the bacteria described do not correspond with one another, and the pathological significance is doubtful. Johne has published a review of the works published up to the present time on foot-and-mouth disease.[¶]

9. According to Rivolta and Johne,[**] and Rabe,[††] there occurs in horses a peculiar tumor-like growth of the connective tissue, called by Johne *mycofibroma* or *mycodesmoid*, which is caused by a micrococcus that grows in the animal tissues in round or grape-cluster-like colonies. These quickly become surrounded by a hyaline capsule, and are therefore to be reckoned as ascococci (*Micrococcus ascoformans*). The tumefaction consists, similarly to that of actinomycosis, of connective tissue, inclosing small foci of proliferation, which break down into pus. The foci harbor the fungi. They seem to develop oftenest in the spermatic cord, after castration. They appear, however, in other parts of the body.[‡‡]

10. According to Eberth[§§] and M. Wolef[‖‖] a large number of the gray parrots (*Psittacus erithacus*) imported into Europe die of a *Streptococcus mycosis*. The micrococci are present in nearly all the organs, but especially in the capillaries of the liver and their neighborhood, where they cause necroses of the liver-cells, but no suppuration.

11. According to Eberth,[¶¶] some of the pseudotuberculous processes occurring in guinea-pigs represent a chronic suppuration that is produced by cocci, and that sometimes leads to metastases in other organs.

2. *The Bacilli and the Morbid Processes Caused by Them.*

(*a*) *Vegetative Forms and Method of Multiplication of the Bacilli.—Non-pathogenic Saprophytic Bacilli.*

§ 173. At present all those bacteria which form rods by their growth and reproduction are classed under the term **bacilli.** Consequently the *microbacteria* (according to the classification of Cohn), as well as the *desmobacteria* designated *bacilli*, are included under this conception.

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[*] "Sur l'hémoglobinurie bactérienne du bœuf," *Compt. rend. de l'Acad. des Sciences de Paris*, cvii., 1888; *Virch. Arch.*, 115. Bd.; and *Annal. de l'Instit. de Pathol. à Bucarest*, 1890.

[†] *Centralbl. f. Bakt.*, iii., 343.

[‡] *Centralbl. f. d. med. Wiss.*, 1886.

[§] "Ueber einen bakter. Befund bei Maul- u. Klauenseuche," *Centralbl. f. Bakt.*, xi., 1892.

[‖] "Bakt. Untersuch. bei Maul- u. Klauenseuche," *Arb. aus dem Reichsgesundhesitamt*, viii., 1893.

[¶] *Deutsche Zeitsch. f. Thiermed.*, xix., 1893.

[**] *Deutsche Zeitsch. f. Thiermed.*, xii., and *Bericht über das Veterinärwesen im Königr. Sachsen f. das Jahr* 1885.

[††] *Deutsche Zeitsch. f. Thiermed.*, xii.

[‡‡] Kitt, "Der *Micrococcus ascoformans* und das Mykofibrom des Pferdes," *Centralbl. f. Bakt.*, iii., 1888.

[§§] *Virch. Arch.*, 80. Bd.

[‖‖] *Virch. Arch.*, 92. Bd.

[¶¶] *Virch. Arch.*, 100. Bd.

The bacilli multiply by division. The rods grow in length and divide into approximately equal parts by the appearance of a transverse wall of division. If the division of the rod that is growing out in length does not take place for some time, or if the division between the different parts is not easily recognized, there result long jointless rods or threads (Fig. 337, *b*). If the divided rods remain hanging together they form chains of rods (Fig. 336, *c*, and Fig. 337, *c*). In many forms of bacteria the ends are blunt, in others rounded or even pointed.

Fig. 336.

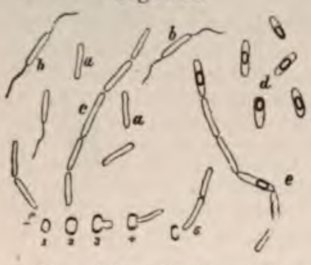

Fig. 337.

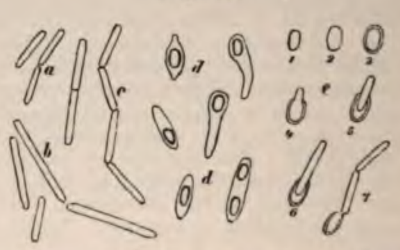

FIG. 336.—*Bacillus subtilis* in different stages of development. (After Prazmowski.) *a*, Separate rods; *b*, Rods with flagella; *c*, Chains of rods; *d*, Separate cells with spores; *e*, Chains of rods with spores; f_1–f_5, Germination of spores. (Magnified 800 diameters.)

FIG. 337.—*Clostridium butyricum*. (After Prazmowski.) *a*, Short rods; *b*, Long rods; *c*, Chains of rods; *d*, Cells with spores; e_1–e_7, Germination of spores. (Magnified 800 diameters.)

In many bacilli resting stages as well as swarming stages are observed, in which the flagella serve as organs of locomotion (Fig. 336, *b*). The flagella are situated sometimes at the ends, sometimes on the sides of the rods, and may occur in large numbers.

In many bacilli endogenic **spore-formation** is observed (Fig. 336, *d*, *e*, and Fig. 337, *d*), in which the spore sometimes lies in the middle, sometimes in the end of the cell. Not infrequently the spores appear in jointed threads. The germination of spores results in the formation of new rods (Fig. 336, f_1–f_5, and Fig. 337, e_1–e_7).

A noticeable change of shape does not usually take place in the rods in spore-formation. In other cases the rods assume a spindle shape or club shape or pear shape (Fig. 337, *d*), and this has been taken as ground for establishing a special group, **clostridium.** Numbers of authors, nevertheless, reckon these forms also with the bacilli.

In the non-pathogenic bacilli spore-formation and germination have been more exactly studied, especially in *Bacillus subtilis* and *Bacillus amylobacter*, and these offer good examples of the processes which come under consideration in this connection.

Bacillus subtilis is a fission-fungus whose spores are very widely distributed in the air, and consequently is met with on various objects. It can be obtained by leaving an infusion of hay open in the incubator. Cultivated upon slices of potato or upon dung of herbivorous animals, it forms whitish-yellow clumps; on liquids, thin and thick pellicles. It requires oxygen for its development.

The fully grown cells (Fig. 336, *a*) are 6 μ long. The snake-like motions sometimes seen are produced by one or two flagella (*b*). The growth of the rods is at first in the form of undivided threads; when these are segmented chains of bacilli are formed. The separate cells may develop in their interior glistening, sharply contoured spores (*d*, *e*), which lie either in the middle or nearer to one end. Subsequently the cells out of which the spores have been formed perish. In germination the spore (Fig. 336, f_1–f_5) becomes pale and loses its glistening appearance and its sharp contour. Then at each pole a shadow appears, while the spore begins a tremulous motion. After a time the contents of the spore project from the side of the membrane in the form of a germinal diverticulum, which becomes elongated, divides, and produces swarming staves. The empty spore membrane may remain preserved for a time after the exit of the embryo.

Bacillus butyricus (*Bacillus amylobacter* of van Tieghem, *Vibrion butyrique* of Pasteur, *Clostridium butyricum* of Prazmowski) possesses staves of 3 to 10 μ in length, and also produces threads and chains of rods. In spore-formation the cells become spindle-shaped or club-shaped and tadpole-shaped (Fig. 337, *d*), and then produce one or two glistening spores. In germination after absorption of the spore membrane a germinal tubule protrudes from one of the two poles (Fig. 337, e_1–e_7). This becomes prolonged and forms new staves by segmentation.

Bacillus butyricus needs no oxygen for its development, and produces butyric-acid fermentation, with evolution of carbonic-acid gas, in solutions of starch, dextrine, sugar, or glycerin. In starch or glycerin or nutrient fluids containing cellulose the bacilli stain blue with iodine.

§ 174. **Saprophytic bacilli** cause many kinds of fermentation by their growth in nutrient fluids; many of them also form pigments.

Bacillus prodigiosus grows on potatoes and bread, as well as on agar-agar and nutrient gelatin. It liquefies the latter, and produces a red coloring-matter which is soluble in alcohol. The coloring-matter develops only where oxygen is present. In the growth in milk the coloring-matter is contained in the fat-droplets. The bacilli themselves are always colorless.

Bacillus fluorescens liquefaciens produces in gelatin whitish cultures, and in the neighborhood of these the gelatin becomes liquefied, while the gelatin in the more remote surrounding portions fluoresces with a yellowish-green color.

Bacillus cyanogenes (Neelsen, Hueppe), when cultivated in sterilized milk, produces a slate-gray color that changes to intense blue on the addition of acid. In unsterilized milk, where lactic-acid bacteria develop simultaneously, the blue color appears without the addition of acid. On potatoes it forms yellowish slimy cultures, in the neighborhood of which the substance of the potato is colored grayish blue (Flügge).

Bacillus acidi lactici causes fermentation of sugar of milk in lactic acid, and produces coagulation of casein. The cultures obtained in gelatin are of a white color.

Bacillus caucasicus (*Dispora caucasica*) forms one of the fungus conglomerates that is called kefyr ferment, which the inhabitants of the Caucasian Mountains use in the preparation, from milk, of the alcoholic drink called kefyr. The kefyr ferment consists of small granules which contain yeast-cells along with rods. The bacilli occasionally show motile forms and develop on the ends of each rod a round spore. By their growth in the milk the milk-sugar is probably converted into glucose, while the yeast-cells produce alcoholic fermentation. According to Hueppe, the kefyr granules contain still other bacteria that peptonize casein.

Hauser described, under the name of **Proteus vulgaris**, a form of bacillus which very often occurs in putrefying animal substances and causes the foul putrefaction. It forms staves of very varied length, and produces when cultivated in meat (Carbone) æthylendiamine, gadinin, and trimethylamine, of which the first two bases are poisonous for animals. According to observations of Bordoni-Uffreduzzi, Foà, Bonome, and Banti, certain bacilli closely resembling the proteus of Hauser seem to be pathogenic for human beings and capable of causing blood infection as well as intestinal affections.

Bacillus aceticus (*Mycoderma aceti*) is a bacillus which converts the alcohol of fermented beverages into vinegar.

Bacillus pyocyaneus occurs occasionally in bandages from suppurating wounds, and causes a greenish-blue discoloration. The bacilli are small and slender. The cultures show different forms of growth. Gelatin is liquefied and turned green. The coloring-matter called pyocyanine is soluble in chloroform and crystallizes out of solution in long blue needles. The bacillus is pathogenic for rabbits, guinea-pigs, pigeons, and frogs, and causes on inoculation sometimes local ulceration, sometimes general infection. According to Kossel, it is pathogenic for children and causes inflammation.

Bacillus saprogenes was discovered in foul-smelling secretions by Rosenbach, who showed that the bacilli cause a foul-smelling putrefaction in meat.

Bacillus ureæ, a short, rather broad rod, is often found, according to Leube, in old urine, and converts the urea into carbonate of ammonia.

A fission-fungus from the cavity of the mouth, described as **Leptothrix buccalis**, forms long, thin, not visibly jointed threads, which are often mixed with cocci, and form masses that stain violet when treated with iodine and acids. According to observations of Traube, Leyden, and Jaffe, it also occurs in gangrenous lung-tissue. Förster, O. Graefe, and Cohn observed it in concretions of the tear-passage. It is assumed by many authors to be the cause of caries of the teeth. Very likely leptothrix represents merely the thread form of different bacteria.

Formerly *Bacterium termo* was named as one of the most familiar forms of bacteria. It was described as a small rod, somewhat constricted in the middle, from 1 to 1.5 μ in length; sometimes glistening, sometimes black, according to the focussing of the microscope; sometimes at rest, sometimes in more or less active motion. According to Hauser, however, *Bacterium termo* merely represents a form of growth of proteus, and can therefore no longer be regarded as a separate species.

(*b*) *Pathogenic Bacilli.*

§ 175. **Bacillus anthracis** (*Bactéridie du charbon*) is the *cause of anthrax*, an infectious disease which occurs mainly in cattle and sheep, but which is occasionally transferred to human beings. It is a fission-fungus that can multiply inside the tissues as well as in the blood when inoculated into a susceptible animal organism.

The anthrax-bacilli (Fig. 338) are from 3 to 10 μ long and from 1 to 1.5 μ broad. In the blood of animals dead of anthrax they lie separate or in thread-like jointed bands [illegible] two to ten staves. The ends are as a rule sharply cut acr [illegible] 339), more seldom slightly concave or even convex (Johne). According to Serafini, Günther, and Johne, they possess a gelatinous capsule, which can be best made visible in dried preparation by staining with methylene blue (Günther). They can be cultivated upon blood-serum, upon gelatin, in bouillon, on slices of potatoes and turnips, in infusions of pease and mashed seeds of different kinds, in the presence of oxygen. They grow most quickly at a temperature which varies from 30° to 40° C. Development is impossible at a temperature below 15° C. and above 43° C.; it is also impossible in the absence of oxygen.

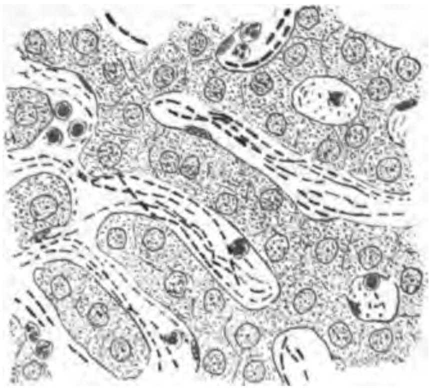

FIG. 338.—Section of liver with capillaries containing numbers of anthrax-bacilli and a few leucocytes. (Preparation treated with gentian violet and vesuvin. Magnified 300 diameters.)

If the conditions above mentioned are present, the staves grow in length (Fig. 339), and may, in a few hours, form threads of considerable length, devoid of membranes. These are made up of short segments that are rendered visible only by treatment with iodine or with some coloring-material (Fig. 339). Ten hours later the clear contents of the threads become granular, and at regular intervals bright glistening bodies become apparent, which enlarge into strongly refractive spores (Fig. 339). Later on, the threads disintegrate and the spores become free.

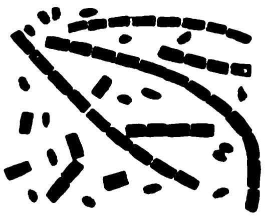

FIG. 339.—Anthrax-bacilli containing spores, and free spores that have escaped from the bacilli. (Cover-glass preparation treated with fuchsin and methylene blue, from a culture of the bacilli on a potato, under the stimulation of heat in an incubator.)

According to Brefeld, Prazmowski, Klein, and others, the spore consists of a protoplasmatic centre which is surrounded by a double membrane, the exosporium and the endosporium. In germination the former is ruptured and the latter becomes the membrane of the liberated embryo. The liberated embryo multiplies by division.

Swarming is not observable during the entire process of development: the bacilli are always motionless.

The anthrax-bacilli easily die under the influence of high temperatures, when subjected to drying, and in the presence of a nutrient medium which has become putrefied. The spores, on the contrary, are very resistant, and consequently are the ordinary medium of the transfer of the disease.

Colonies in gelatin show a wavy, irregularly shaped margin, and consist of wavy, curly bands of threads that subsequently grow out of the culture in various directions. The gelatin becomes liquefied in the immediate neighborhood of the culture. On slices of potato they form grayish-white cultures that appear slightly granular (Plate I., Fig. 5), with distinct outline. They form a whitish coating on blood-serum.

Stab-cultures in gelatin are white, and in the process of growth they radiate at right angles from the track of inoculation, especially near the surface. After liquefaction of the gelatin they sink to the bottom.

If the bacilli or spores get into the blood they multiply and produce the staves above described, which can be readily observed in a drop of blood taken from a vessel and stained with gentian violet. On decolorizing the preparation by Gram's method it will be found that these staves retain the stain. Sections of hardened organs show that they are present in large numbers in the capillaries, especially of the spleen, of the liver, of the lungs, and of the kidneys. The contiguous parenchyma of the tissue usually appears unchanged; still the local growth of the bacilli may produce degeneration of tissue and necrosis, especially in the spleen-pulp. If an infection of the blood takes place during pregnancy the infection may go over to the fœtus.

If anthrax-bacilli or their spores get through little wounds of the skin

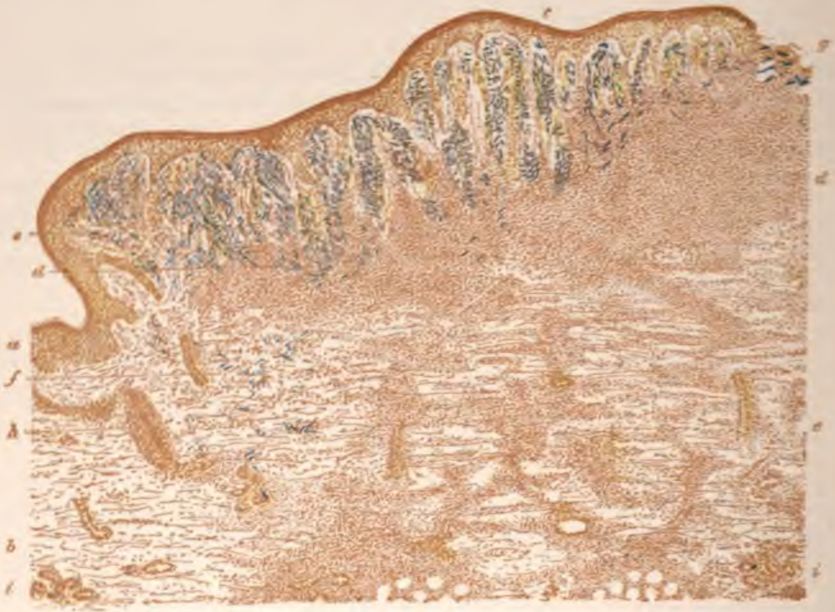

FIG. 340.—Section through an anthrax-pustule ten days old, extirpated from the arm of a man. *a*, Epidermis; *b*, Corium; *c*, Papillary body, œdematous, swollen, filled with exudate and bacilli; *d*, External layer of the corium infiltrated with cells; d_1, The same containing bacilli; *e*, Deeper layers of the corium containing bands of cells; *f*, Tissues of the skin interspersed with bacilli and cells; *g*, Bloody exudate on the surface containing bacilli; *h*, Hair-follicle; *i*, Sweat-gland coil. (Preparation hardened in alcohol, treated with gentian violet, iodine, and vesuvin, and mounted in Canada balsam. Magnified 35 diameters.)

in human beings they develop a somewhat elevated pustule with arched or flattened surface (Fig. 340), usually from six millimetres up to several centimetres in diameter. The pustule is red or possibly more of a yellowish color. It is often, in time, covered with vesicles, or after the loss of epithelium it becomes moist; and by the drying of this exudate, which is often bloody, a scab is formed (Fig. 340, *g*). Infection takes place in persons that butcher or bury, or prepare the skins of animals affected with anthrax; occasionally, also, it is conveyed through the sting of a fly that has taken up the blood of an animal affected with anthrax.

The centre may become depressed by the formation of the scab in the middle, the edges forming a wall around. The neighborhood of the pustule is sometimes little changed and sometimes red and swollen, and may be occupied by small yellowish or bluish-red vesicles (W. Koch). If the process remains local the sloughing pustule may be thrown off. Infection of the blood is followed by fatal consequences. In rare cases infection shows itself in a wide-spread, intense œdematous swelling of the tissues without the formation of a circumscribed pustule.

In the region of a fully developed anthrax-pustule (Fig. 340) the corium (d, d_1) and papillary body (c) become permeated by a cellular serous and bloody exudate as well as by bacilli. The bacilli lie in the external portions of the corium (d_1) and in the papillary body (c); but they can penetrate into the deeper layers of the corium (f). In the region of the papillary body (c) the exudate is sanguinolent. Vesicles filled with bloody fluid result if the exudate extends up to the epithelial covering and if the deeper portions of the lâtter become liquefied, thereby permitting the superficial portions to be lifted up by the exuded fluid. If the upper layers of skin are lost the bloody fluid containing bacilli (g) appears on the surface.

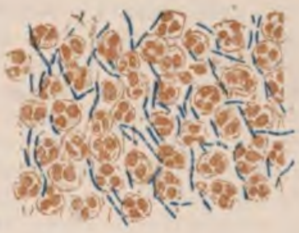

FIG. 341.—Section from a portion of an anthrax-pustule where the tissues contained bacilli. (Preparation treated according to Gram's method with gentian violet and then colored afterward with vesuvin. Magnified 350 diameters.)

The cellular infiltration has its seat mainly in the corium (d, d_1, e), and it makes the impression as if the great massing of cells would form, to a certain extent, a protection against the further encroachment of the bacteria.

The cells that accumulate are for the most part polynuclear leucocytes (Fig. 339). The taking up of vigorous, strong bacilli into the cells does not take place; consequently the influence of the cells upon the development of the bacilli—if any such influence exists at all—cannot lie in this act of "devouring" on the part of the cells.

If infection with anthrax-spores takes place in the intestinal canal the lesions are usually located in the region of the small intestine, more seldom in the stomach and large intestine, and disease foci are formed which resemble in a general way the pustules on the skin, and which consist of reddish-black or reddish-brown hæmorrhagic foci the size of a lentil or bean, with a grayish-yellow or greenish-yellow discolored slough in the middle. In other cases the crests of the folds of the mucous membrane are swollen and show hæmorrhagic infiltration, and the most prominent parts show evidences of sloughing. The mucosa and submucosa are infiltrated with blood in the region of the foci; the surrounding tissue is œdematous and hyperæmic. In these foci, as well as in their surroundings, the tissue contains bacilli, especially in the blood- and lymph-vessels, and they may be equally well seen in the swollen lymph-glands.

According to observations of Eppinger and Paltauf, primary lung infection occurs by inhalation of anthrax-spores, usually proving fatal in from two to seven days. Individuals that have to handle the hair of animals that have died of anthrax are specially exposed. Rag-sorters' disease, occurring in the rag-sorters in paper-factories, is, in a part of the cases, according to Eppinger and Paltauf, nothing more than an anthrax infection. The bacilli are very probably taken into the lungs in the form of spores with the inspired air, and develop in the bronchi and alveoli, in the spaces that contain the tissue-juices of the lung and pleura, and in the bronchial glands, and they also penetrate into the vessels. Their multiplication causes inflammatory processes in the lung, as well as the pouring out of a bloody serous exudate in the pleural space and in the mediastinal tissues, and swelling of the lymph-glands. It may also lead to formation of necrotic foci in the lung and in the bronchial and tracheal mucous membrane.

Mice, rabbits, sheep, horses, and sparrows are very susceptible to anthrax. White rats, dogs, and Algerian sheep are less susceptible or enjoy complete immunity. Cattle become easily infected through the intestines by taking in the spores into the alimentary canal, but are less susceptible to inoculation. Formation of spores does not take place in the tissues and in the blood

By cultivating the bacilli at 42–43° C. (Toussaint, Pasteur, Koch) it is possible to weaken their activity, so that first sheep are not killed, then rabbits and guinea-pigs, and finally even mice are no longer killed by inoculation. If the temperature is near 43° C., this condition can be reached in six days; at 42° C. it may take sixty days before the virulence becomes weakened to this extent (Koch). By first inoculating with bacilli that kill mice, but are harmless for guinea-pigs, and by a second inoculation with bacilli that will kill guinea-pigs, but not strong rabbits, sheep and cattle can be rendered immune, but not mice, guinea-pigs, or rabbits. Practically, however, this protective inoculation cannot be employed, because it is necessary to inoculate with very virulent material in order to protect from natural infection with spores introduced into the intestines; and consequently a large per cent.—10–15 per cent.—die from the protective inoculation itself. Moreover, the protection is only of short duration, and the inoculation must be repeated in about a year.

According to observations of Roux and Chamberland, the anthrax-bacilli can, while retaining their full virulence, be permanently deprived of the power of producing spores by cultivation in bouillon to which a small amount (1 : 2000) of potassium permanganate or carbolic acid (1–2 : 1000) has been added.

The bacilli of anthrax only develop at a temperature above 15° C., and in the presence of oxygen. In the body of an animal buried more than one metre deep, no spores can form. According to Johne,* they do not develop in the animal body even at higher temperatures. This, however, can take place very readily, according to Koch, if, in burying animals dead of anthrax, the blood and secretions (urine) get on the surface of the ground, where the temperature in summer goes above 15° C.

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* *Bericht über das Veterinärwesen im K. Sachsen pro* 1885.

Pasteur's assertion[*] that earthworms bring the spores of the bacilli in their intestinal canal up to the surface from the bodies of animals that have been buried, and deposit them with their excreta, is declared by Koch to be improbable, and unnecessary for the explanation of the spread of anthrax, since in burying the bodies the surface-layers of the soil become contaminated. Koch bases his statement upon experiments made to test this point. It is evident from Koch's investigations that the transfer by earthworms does not play the rôle attributed to it by Pasteur, but the possibility is not entirely excluded. Bollinger was able to detect the presence of the bacilli—by means of inoculations—in only one specimen among seventy-two earthworms taken from pastures where anthrax prevailed.[†]

According to Koch, anthrax-bacilli can be cultivated on potatoes and alkaline or neutral infusions of hay, on cold infusions of pea-straw, on mashed barley and mashed wheat, in the juice of turnips, wheat, leguminous seeds, and numerous dead plants, in the presence of a sufficient quantity of water. Consequently the bacilli grow and develop outside the body—e.g., in marshes and on river-banks (R. Koch). The entrance into the animal body is to be regarded as an occasional excursion of the ectogenic bacillus.

According to Soyka, the development of spores takes place very quickly in a moist medium containing the necessary nutrient material. According to Kitt, cattle-dung forms a nutrient substratum for the bacilli.

§ 176. The **Bacillus typhi abdominalis** (Fig. 342) is a fission-fungus which appears mostly in the form of plump staves 2 to 3 μ long, with rounded ends growing out into long pseudothreads in cultures. It is recognized as the cause of typhoid fever. When examined alive in cultures it shows lively independent locomotion, caused by from eight to twelve flagella which are attached to the sides of the staves as well as to the ends. The flagella can be made visible by proper staining methods. The bacillus was first observed and described by Eberth and Koch, and afterward cultivated pure by Gaffky. A. Pfeiffer showed its presence in the dejecta of typhoid patients, and his observations have been corroborated often since (Fränkel, Simmonds, Seitz, Chantemesse, Widal, and others). According to Seitz, Hueppe, Neumann, and others, it may also be present in the urine of typhoid patients.

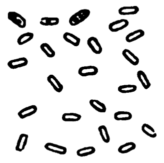

FIG. 342.—Bacillus of typhoid fever. (Magnified about 800 diameters.)

It may be well stained in cover-glass preparations with gentian violet, alkaline methylene blue, and Bismarck brown. The bacilli stained with gentian violet become decolorized by treatment with iodine according to Gram's method. The detection of the bacilli in sections of hardened organs is somewhat difficult, because the cell-nuclei also become stained, and because the bacilli are not uniformly distributed, but usually lie in clumps in the tissue.

The bacillus may be cultivated as well in nutrient gelatin, agar-agar, and blood-serum as in milk and on slices of potato. It forms a coating on the latter that is scarcely recognizable with the eye. But if the surface is touched with a platinum wire it becomes apparent that it is covered with a pellicle, and the microscopic examination shows that this consists of bacilli.

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[*] *Bulletin de l'Acad. de Méd.*, 1880, No. 28.

[†] *Arb. a. d. path. Inst. zu München*, 1886.

On gelatin and agar-agar the bacilli form whitish-gray flat cultures of irregular shape. *Gelatin is not liquefied.* Milk in which the bacilli are grown is not changed externally.

Cultures flourish at room-temperature as well as at body-temperature. Ordinary potato-cultures kept between 30° and 42° C. produce staves which have glistening granules in their poles. Gaffky interpreted these granules as spores, and formerly most authors accepted this interpretation. According to Buchner and Pfuhl, however, these granules at the poles are not spores, but are degeneration forms occurring especially where the culture contains an acid (Buchner), in the presence of which the staves become relatively long. The polar granules represent condensed protoplasm, and consequently stain in fresh preparations more quickly with the aniline dyes than do the other parts. The clear, colorless flakes on the ends of the staves that are seen on dried and stained bacilli, and which were regarded as identical with the polar granules and declared to be spores, result, according to Buchner, from the formation of hollows in the ends of the staves, due to retraction of the tube of protoplasm on the death and drying of the bacilli. The polar granules become changed in position to the middle portions by this retraction. Consequently spore-formation has not been proved to exist.

In moist earth (Grancher, Deschamps), in pure and impure water, typhoid-bacilli may remain alive for weeks. They do not die out for many weeks in artificial Seltzer water (Hochstetter). In privy-vaults and fæcal masses, or in earth saturated with fæcal matter, they may survive, under certain circumstances, for weeks and months (Finkler, Uffelmann, Karlinski).

Inoculation of the bacilli in animals used ordinarily for experimental purposes does not produce a disease corresponding to typhoid fever in man. Still experiments of Sirotinin, Beumer, Peiper, and others have shown that the typhoid-bacilli produce active toxins and toxalbumins (Brieger) which kill animals in larger doses, causing hyperæmia and swelling of the intestinal follicles, of the mesenteric glands, and of the spleen. Cultures injected into the tissues produce locally more or less severe inflammation.

Outside of the human body the bacilli have been found, as already stated, in the dejecta of typhoid patients, and they have been found, furthermore, in suspected water (Chantemesse, Widal, Beumer, Thoinot, Martinotti, Barbacci) and in the soil (Macé, Uffelmann).

The bacilli or their spores get into the human organism probably with the drinking-water and food; still an infection through the lungs is not to be excluded. According to the results of the anatomical examination, they develop in the wall of the intestines, in the region of the solitary and of the agminated follicles of the small and large intestines, as well as in the mesenteric lymph-glands and in the spleen. In the first of these localities they cause an inflammatory infiltration of the mucosa and submucosa, that is extraordinarily rich in cells (Fig. 343, a_1, b_1), and appears in the form of flat or somewhat elevated and rounded areas above the inner surface of the intestines. Occasionally cellular inflammatory foci limited in area occur also in the muscularis (c_1) and in the serosa (d_1). A part of the infiltrated tissue usually sloughs and is then cast off, so that ulcers are formed. In another part the swelling may subside by the absorption of the infiltration.

The swelling of the lymph-glands, which is also due to the accumulation of cells and fluid, either ends in recovery by the absorption of the infiltration, or leads to partial necrosis of tissue. In the spleen the pulp, in particular, swells, while its vessels are greatly dilated with blood, and later its parenchyma becomes crowded full of cells and fluid.

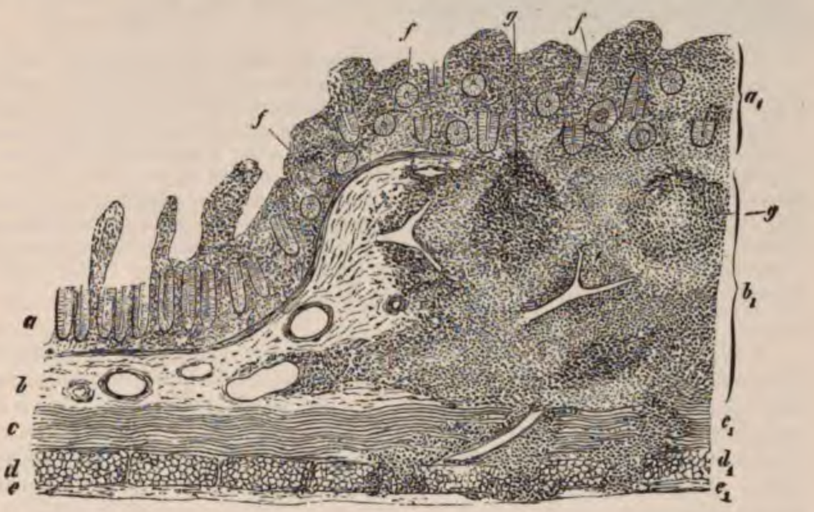

FIG. 343.—Typhoid fever. Section through the edge of a swollen Peyer's plaque. *a*, Mucosa; *b*, Submucosa; *c*, Muscularis interna; *d*, Muscularis externa; *e*, Serosa; a_1, b_1, c_1, d_1, e_1 The different layers of the intestine infiltrated; *f*, *f*, Sections of a Lieberkühn's gland; *g*, Follicle. (Preparation hardened in alcohol, stained with Bismarck brown, and mounted in Canada balsam. Magnified 15 diameters.)

According to recent investigations, the bacilli are usually distributed to other parts of the body, and it is probable that the inflammatory exudates in the lung which occasionally appear in the course of typhoid fever, depend in part upon the growth of the bacilli in the lung. Still it must be borne in mind that inflammations due to inhalation of irritating substances very often occur in the lungs of typhoid patients, and also that *secondary infections* with cocci start from the ulcers and may cause metastatic inflammations in the different tissues. The swellings of the mucosa and submucosa and of the perichondrial tissue in the palate, throat, and larynx that often occur, and that depend upon inflammatory infiltration, are partly the consequences of specific infection and partly of secondary disease. The bacilli have often been discovered in the liver (Gaffky, E. Fränkel, Cygnäus, Simmonds), also in the gall-bladder (Chiari). The bacilli do not usually circulate in the blood; nevertheless, Neuhauss and Rütimeyer were able to cultivate them from the blood of roseola patches. According to Seitz, Neumann, Faulhaber, and others, they may often be found in the kidneys. They have been observed by others (Chantemesse, Widal, Curschmann) in the central nervous system, by Ebermaier in the inflamed periosteum, by Tavel in the inflamed testicle, by Valentini in purulent pleuritic exudate, by A. Fränkel in the exudate in peritonitis. According to Quincke, they seem to be almost constantly present in the marrow of bones. Neuhauss was able to find them in the spleen of a fœtus four months old whose mother was suffering from typhoid fever and had an abortion. Reher, Eberth, Chantemesse, Widal, and Ernst make similar statements.

Since the typhoid-bacilli produce active toxins and toxalbumins, the morbid phenomena are to be referred largely to poisoning.

The cultures of typhoid-bacilli show few characteristic properties, and are consequently difficult to distinguish from other widely distributed bacteria. Thus their properties are very similar to those of the *Bacillus coli communis* (cf. § 177). As a differential mark, it is asserted that the typhoid-bacilli produce no indol, whereas other similar bacteria—for instance, the *Bacillus coli*—produce indol, so that the cultures of the latter turn red on the addition of potassium nitrite and sulphuric acid. In two per cent. grape-sugar bouillon the typhoid-bacillus produces no gas, whereas the *Bacillus coli* develops gas. Finally, the typhoid-bacillus produces faint acidity in milk, but no coagulation; whereas the *Bacillus coli* causes strong acidity and curdling of the milk in from twenty-four to forty-eight hours at 37° C.

§ 177. The **Bacillus coli communis**, or the *Bacterium coli commune* (Escherich), is a fission-fungus constantly present in the abdominal canal of man as well as mammalian animals. The bacilli are staves 2 to 3 μ long and .3 to .4 μ thick. They are capable of locomotion by means of flagella, which may number as high as twenty on one staff (Bunge, Luksch, Günther). The bacilli grow at room-temperature as well as at the temperature of the incubator. In the depth of the gelatin they form small, round white colonies, on the surface pellicle-like colonies. On potatoes a yellow juicy coating is formed, the shade of maize or pease (Günther). Spore-formation does not occur. The bacilli cannot be stained by Gram's method.

The *Bacillus coli* is very similar to the typhoid-bacillus; still it may be distinguished from this by proper methods of cultivation and by the employment of suitable reactions (cf. § 176). Formerly it was regarded as a harmless saprophyte of the large intestines, but it can no longer be doubted, according to recent investigations, that pathogenic properties are also attributable to it. Thus, under suitable conditions, such as perforation or incarceration of the intestines, or impacted fæces, it may get into the peritoneal cavity and cause purulent inflammation, or at least take part with other bacteria in the production of inflammation. It gets, moreover, not infrequently, into the gall-ducts and gall-bladder, and seems capable of causing inflammations of varying intensity. Moreover, the bacillus has also been found, in some cases of septic disease, in the exudate of the membranes of the brain; furthermore, in pericarditis, pyelitis, cystitis, bronchopneumonia, strumitis, and scarlatinal angina.

The similarity between the *Bacillus coli* and the typhoid-bacillus has caused various authors to assume that the two bacilli represent only varieties of one kind, and that consequently the two forms may pass over into each other. Still, at present the opinion prevails that the two bacilli are to be entirely separated from each other (cf. § 176). As there are other bacilli that much resemble the *Bacillus coli*, and often are not to be distinguished with certainty from it, it may well be assumed that the publications on the *Bacillus coli* have not always dealt with the same bacterium.

§ 178. The **Bacillus pneumoniæ** is a bacillus discovered by Friedländer and Frobenius; it is capable of producing *croupous pneumonia*, but is present only in a limited number of cases of this disease (cf. § 171). Moreover, it has also been found in the nasal secretion and in inflammations of the middle ear.

The bacilli lie in the alveolar exudate, as well as in the pleuritic exudates that form at the same time as the inflammation of the lungs. They appear sometimes in the form of staves (Fig. 344, *b*), sometimes in the form of oval cells (*a*), and not infrequently they are joined together so as to form short chains. Since the oval cells are more numerous than the staff forms, the bacillus was originally reckoned with the cocci.

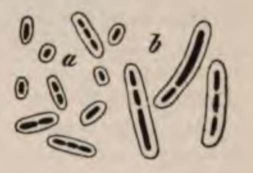

FIG. 344.—*Bacillus pneumoniæ* of Friedländer. *a*, Oval cells and rows of cells with gelatinous capsule; *b*, Staves with gelatinous capsule. (Magnified 500 diameters.)

The bacilli possess a hyaline, mucin-like capsule, soluble in alkalis, insoluble in acetic acid, which forms a common sheath around the chains of the bacilli (Fig. 344). Independent motion has not been observed.

The bacillus loses its color when stained with gentian violet and treated with iodine and alcohol, and may be easily distinguished in this way from the diplococcus. In order to stain it along with the capsule in sections, Friedländer recommends the employment of an acid solution of gentian violet, consisting of 50 parts of concentrated alcoholic solution of gentian violet, 100 parts of distilled water, and 10 parts of acetic acid. After staining for twenty-four hours the sections are washed out in a 0.1 per cent. solution of acetic acid for a short time.

The bacilli grow in nutrient gelatin at room-temperature, and form porcelain-white knob-shaped cultures on the surface of the gelatin. The oval and staff-shaped cells possess no capsule. Stab-cultures in gelatin are nail-shaped (Fig. 345), this appearance being due to the fact that the bacilli form a knob-shaped prominence at the entrance of the canal of inoculation. This is a peculiarity that the pneumonia-bacilli share with many other bacteria. On blood-serum they form gray transparent colonies, on agar-agar grayish-white, on potatoes grayish-white or yellowish-white, creamy colonies. Spore-formation is not observed.

Rabbits are almost entirely refractory to inoculation of the lung; mice, on the contrary, die with pleurisy and disseminated pneumonia in from eighteen to twenty hours after injection of the bacilli into the lung, and the exudate as well as the blood are found to contain bacilli with gelatinous capsule, some lying free, some inclosed in cells. A typical lobar pneumonia cannot be produced in the ordinary experimental animals.

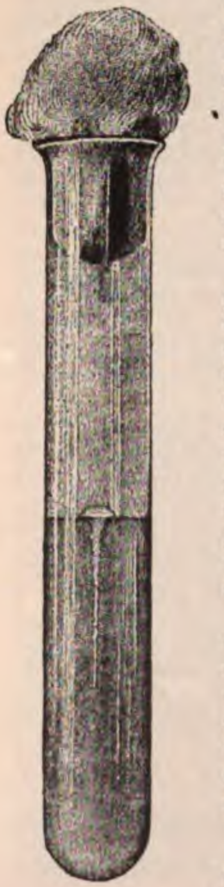

FIG. 345.—Nail-shaped stab-culture of Friedländer's pneumococcus in gelatin.

Neumann[*] found, in a case of pneumonia that occurred in the course of an attack of variola, a bacillus which he regards as identical with that which has been described by Schön as occurring in vagus-pneumonia of rabbits, and which is called by Flügge *Bacillus pneumonicus agilis*.

Affanasiew[†] found, in ten cases of whooping-cough, in the mucus that was coughed up, a small bacillus which he regards as the cause of whooping-cough. Ssemetschenko[‡] published a similar discovery.

§ 179. A bacillus was described in 1892 by R. Pfeiffer as the **influenza-bacillus,** and the discovery has been frequently corroborated since (Weichselbaum, Kruse, Bäumler, and others); it is regarded as the cause of the influenza. In individuals who are sick of influenza it is found in the catarrhally affected air-passages, occasionally also in the lungs. The small bronchi may contain enormous numbers of the bacilli in pure culture. It is assumed that the multiplication of these organisms in the respiratory tracts causes inflammation, and that at the same time they produce poisons which on being absorbed cause the morbid phenomena peculiar to influenza. Canon states that the bacilli go over into the blood.

The influenza-bacilli are very small, thin staves with rounded ends, which lie separate or joined in twos, and may be stained with the usual aniline dyes, but not by Gram's method. They may be cultivated at body-temperature upon blood-agar or on agar that is smeared with human or pigeon's blood, and they form small, drop-like colonies as clear as water. They do not grow, on the contrary, upon the other usual media. Spore-formation is not observed. In apes a catarrhal inflammation of the respiratory passages can be produced by intratracheal injection of pure cultures. Rabbits may be poisoned by inoculation of cultures, and they acquire, in consequence of the poisoning, a paralytic weakness of the muscles and dyspnœa.

§ 180. The **Bacillus diphtheriæ** is a bacillus, first accurately studied by Löffler, which is found in the croupous membrane that occurs in diphtheria, and is very probably the cause of diphtheria. In the internal organs, such as the spleen and lymph-glands, the bacilli are either entirely absent or they are present in such small numbers that they can only be detected by methods of cultivation (Frosch).

They have the same length as the tubercle-bacilli, but are about twice as thick and are often swollen at the ends. Their substance has a granular appearance. For staining it is best to use a staining solution of 30 ccm. of a concentrated alcoholic solution of methylene blue in 100 ccm. of potassium-hydrate solution of .0001 per cent. strength. After staining, the sections are put into .5 per cent. acetic acid for a few seconds and afterward treated with alcohol. The bacilli are often segmented in stained preparations.

The diphtheria-bacilli grow best, according to Löffler, on a mixture of 3 parts calf's or sheep's blood-serum and 1 part neutralized calf-bouillon to which 1 per cent. peptone, 1 per cent. grape-sugar, and .5 per cent. salt have been added; or upon blood-serum or agar-agar with 10 per cent. glycerin or nutrient bouillon containing sugar (Kolisko, Paltauf, Kitasato). They form grayish-white colonies. They require a temperature above 20° C. for their development. Löffler found the dried bacilli still capable of living after one hundred and one days. Roux and Yersin succeeded in obtaining cultures of the bacilli, that were still virulent, from a three months' old diphtheritic membrane that was dry and had been protected from the light. Spore-formation has not been observed.

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[*] "Zur Kenntniss des *Bacillus pneumonicus agilis*," *Zeitsch. f. klin. Med.*, xiii., 1887.

[†] "Aetiolog. u. klin. Bakteriologie des Keuchhustens," *St. Petersb. med. Wochensch.*, 1887.

[‡] "Zur Frage der Keuchhustenbakterie," *St. Petersb. med. Wochensch.*, 1888.

Guinea-pigs inoculated subcutaneously with cultures of the bacilli (Löffler, Roux, Yersin) die in two or three days. At the point of inoculation there is found a whitish deposit and hæmorrhagic œdema. The point of inoculation contains bacilli; the internal organs, on the contrary, are free.

In rabbits, chickens, and pigeons, the introduction of cultures into the trachea through a wound is followed by the formation of a pseudomembrane. Inoculations of the conjunctiva in rabbits and of the vagina in guinea-pigs, is also followed by the formation of a false membrane. In young rabbits a simple smear upon the conjunctiva, which need hardly be injured, suffices to produce death with high fever and nervous phenomena (Babes).

Roux, Yersin, Löffler, Spronck, and others observed subsequent paralysis in pigeons and guinea-pigs that had survived inoculation. Roux and Yersin assert that intravenous injection of filtered cultures—i.e., bouillon-cultures containing no bacilli—causes, in guinea-pigs and rabbits, a severe illness characterized by paralysis, and fatal consequences in two or three days. Löffler obtained a substance precipitable with alcohol from cultures of the diphtheria-bacilli which he had treated with glycerin. When it is repeatedly thrown down and purified with alcohol from solution it forms a whitish precipitate, that causes an inflammatory hæmorrhagic œdema and necrosis of the skin when injected in aqueous solution under the skin of rabbits in small doses (.1 to .2 gramme.). According to the investigations of Brieger and C. Fränkel, the substance which the bacilli produce is a poison that closely resembles the *toxalbumins* in its chemical relations, and in the pure state is fatal to experimental animals, in a dose of 2.5 mg. to 1 kg. of the weight of the animal, often taking effect only after weeks or months. The circumstance must also be mentioned that Guinochet obtained a poison from cultures of the bacilli in urine. Locally the *poison* produces inflammation; when taken up into the juices of the body, it produces an exudate in the pleuræ, nephritis, fatty degeneration of the liver, and paralysis. According to Proskauer and Wassermann, the organs and blood of animals dead of diphtheria from inoculation contain a very poisonous toxalbumin that kills animals on inoculation in from six to twenty-one days. Sheep are very susceptible to diphtheria intoxication.

Diphtheria in man is characterized by an inflammation extending mostly over the mucous membrane of the throat, palate, palatal arches, and the upper respiratory passages. It appears as a febrile infectious disease combined with symptoms of intoxication, and gives rise locally to croupous exudates, partly also to diphtheritic desquamation (cf. § 98, Figs. 155 and 156). The croupous membranes constitute the most striking feature. They are spread over the throat usually in limited flat patches, more rarely uniformly over larger areas, or they may form a continuous lining upon the larynx and air-passages. Underneath the croupous membrane the epithelium is mostly lost, the connective tissue of the mucous membrane hyperæmic, infiltrated, and swollen. In severe cases the superficial layer of connective tissue is necrotic in places, most frequently on the tonsils, which are more or less swollen, often to a very marked degree. Deeper down in the tissues, the lymph-glands, especially those in the neck in near proximity, are swollen, and often show, on microscopic examination, small foci in which the cells are necrotic and disintegrated. Of the internal organs the kidneys especially are usually changed, in that there is a more or less high degree of fatty degeneration in the epithelium and capillary walls, not infrequently, also, an œdematous swelling and foci of small-cell infiltration—conditions which are to be regarded as consequences of the *intoxication*.

The lungs are not notably changed by the diphtheria poison; still bronchopneumonias often occur which are due to inhalation of the irritating contents of the bronchi, or to an extension of the bronchial inflammation upon the respiratory parenchyma. The inflammatory irritants that get into the lungs in this way are usually not the diphtheria-bacilli, but products of the specific exudate which often inclose bacteria, especially cocci, that have become lodged secondarily.

Recently attempts have been made by different experimenters to cure diphtheria after it has broken out, and to make children poison-proof against diphtheria poison, by the injection of an antitoxin. The investigations made by Behring and Ehrlich in this direction have been to a certain extent successful. Sheep, goats, and horses susceptible to diphtheria may be rendered immune by inoculation with cultures in which the bacilli have been attenuated or killed; and the blood, also the milk, of the animals that have been made immune contain an antitoxin which neutralizes the effect of the toxins when injected into the body of an infected animal in certain amounts, and which is able, as they believe, to make human beings and animals poison-proof. Judging from the most recent experiments in this direction, favorable results may indeed be obtained in human beings suffering from diphtheria, but it is impossible as yet to forecast the proportions that these favorable results may assume.

According to Löffler, von Hoffmann, Roux, Yersin, Babes, and others, bacilli designated as *pseudodiphtheria-bacilli* occur very often in the mouth and throat, which look like the diphtheria-bacilli and even in cultures can only with difficulty be distinguished from these. Since the diphtheria-bacilli may lose their virulence, it is not improbable that the two bacilli are varieties of one kind.

§ 181. The **Bacillus tetani** (Kitasato) is a fine, slender bacillus which is widely distributed throughout the superficial layers of the earth, and is to be regarded as the cause of tetanus. According to observations of Nicolaier made in 1885, it is often possible, in mice, guinea-pigs, and rabbits, by a subcutaneous inoculation of earth taken from the superficial layers, to obtain typical tetanus with fatal termination.

The demonstration was first made by Rosenbach in the year 1886 that the bacilli found in traumatic tetanus and those found in tetanus due to frost-bite in human beings, in the region of the seat of injury, were one and the same, and that when inoculated into guinea-pigs and mice they cause genuine tetanus. Since then this discovery has been often corroborated. The bacillus is present neither in the soil nor in the infected wound in an isolated condition, and consequently inoculations have been made with mixtures of bacteria. The effort to isolate in cultures the bacillus that was regarded as the cause of tetanus was unsuccessfully made by most investigators. Kitasato in 1889, in Koch's laboratory, succeeded in isolating the tetanus-bacillus by allowing the mixed cultures to remain in the incubator a few days and heating for a half-hour or an hour at 80° C., and then subsequently making plate-cultures in an atmosphere of hydrogen. The bacteria growing along with the tetanus-bacillus are killed by the heating, while the tetanus-bacillus is preserved.

The tetanus-bacillus (Kitasato) is anaërobic and grows very well in an atmosphere of hydrogen, but not in carbonic-acid gas. It grows in ordinary slightly alkaline agar-agar containing peptone, and in blood-serum and nutrient gelatin. It liquefies the latter with the production of gas. Addition of 1.5–2 per cent. grape-sugar accelerates the growth. The most favorable temperature is between 36° and 38° C. It forms long, thin, bristle-like staves that produce spores on one end which cause a swelling of the end of the staff, giving rise to the name knobbed bacilli. It may grow out in cultures into long pseudothreads. The cultures give out an offensive odor; gelatin is slowly liquefied. The bacilli stain by Gram's method. They are motile except at the period of spore-formation. Pure cultures inoculated into horses, asses, guinea-pigs, mice, rats, and rabbits cause tetanus; but rabbits must be inoculated with somewhat larger amounts. The tetanic contractures start first in the neighborhood of the point of inoculation. Suppuration does not occur at the point of inoculation. The bacilli are not to be found after the animal is dead, and are never found except at the seat of inoculation.

According to the experimental investigations of Kitasato, the filtrate which is obtained from bouillon-cultures of the bacilli, but which contains no bacilli, acts in the same way as the cultures containing the bacilli, and guinea-pigs especially are very sensitive to it. The blood or transudate from the thoracic cavity of an animal infected with tetanus, although free from bacilli, causes tetanus when inoculated into mice. It is consequently to be assumed that in tetanus it is a matter of *intoxication* with a poison (tetanotoxin) that is distributed throughout the blood. The poison is destroyed by heat (Kitasato)—a temperature of 65° C. and over—in a few minutes, and by direct sunlight in from fifteen to eighteen hours, and loses its effects in diffuse daylight in a few weeks. According to investigations of Brieger and Cohn, the purified poison gives no reaction for albumin, and consequently does not belong to the toxalbumins, as was formerly assumed by Brieger and Fränkel.

The **Bacillus œdematis maligni** (*Vibrion septique* of Pasteur) is an anaërobic bacillus which was first thoroughly investigated by R. Koch. It is found in various putrefying substances, and the spores almost never fail to be present in earth that is manured with foul liquids or liquid manure. The bacilli are 3 to 3.5 μ long and 1 to 1.1 μ broad, and often form long pseudothreads. They are similar to the anthrax-bacilli, but are somewhat more slender and rounded on the ends, not sharply cut across, and are occasionally motile. In spore-formation a swelling develops from one part of the rod, as in *Bacillus butyricus*, so that spindle-shaped and tadpole-shaped forms result.

The bacillus is motile and possesses flagella on the ends as well as on the sides. It is not stained by Gram's method.

It grows in nutrient gelatin as well as in agar-agar and coagulated blood-serum, but it must be introduced deep down and cut off from the air. Nutrient gelatin with the addition of 1 or 2 per cent. of grape-sugar is a specially favorable medium (Flügge). Nutrient gelatin and blood-serum are liquefied, the latter with the production of gas.

The bacillus can be readily obtained by sewing up garden-earth under the skin of a guinea-pig and by taking care that the air does not find access to the point of inoculation. The subsequent multiplication of the bacilli causes a progressive œdematous swelling of the subcutaneous tissue. At a more advanced stage the bacilli spread upon the serous membranes, in the spleen, and in other organs.

Mice, guinea-pigs, horses, sheep, and swine are susceptible to the bacilli; cattle are not (Arloing, Chauveau).

According to the observations of Brieger, Ehrlich, Chauveau, Arloing, and others, the œdema-bacilli also occasionally develop in the tissues of human beings, especially when the tissues are poorly nourished and the bacilli by any accident—e.g., by puncture of a hypodermatic syringe—get into the depth of the tissues. They lead to a gangrenous process which is combined with bloody œdema and the development of gas.

According to Vaillard and Vincent, tetanus does not follow inoculation of tetanus-bacilli deprived of poison. Consequently it must be assumed that the bacilli can only multiply in the tissues of man and animals and lead to poisoning when special conditions are present, when the tetanus poison itself is also present at the same time, or when other bacteria, such as *Bacillus prodigiosus*, get into the tissues.

According to investigations of Kitasato, Tizzoni, Cattani, Baquis, Behring, and others, susceptible animals may be made immune from tetanus, or, more properly speaking, poison-proof against the poison of tetanus. The blood of animals that have been rendered poison-proof possesses the property of destroying the poison of tetanus, and consequently it is possible to immunize susceptible animals with the curative serum obtained from this blood, or to cure tetanus that has already broken out in man or animals (cf. § 29).

According to Kolb, Babes, Tizzoni, and Giovannini, the diseases designated as *purpura hæmorrhagica* and as *hæmophilia neonatorum* are to a certain extent caused by a special kind of bacillus that is also pathogenic for animals (cf. § 46). Pianese is of the opinion that *chorea* is caused by a bacillus.

§ 182. The **Bacillus tuberculosis** is the cause of the infectious disease which is very frequent as well in man as in the domestic mammalia, and which is usually called **tuberculosis**, but is also sometimes called *Pearl disease* (*Perlsucht*) in animals.

The tubercle-bacilli, discovered and thoroughly investigated by Koch in the year 1882, form narrow staves (Fig. 346), 1.5 to 3.5 μ in length, that are often slightly curved. Aniline dyes (fuchsin or gentian violet), in aqueous solution with the addition of an alkali or carbolic acid or aniline, are suitable for staining them. The bacilli once stained retain the dye even when the preparation is decolorized with dilute sulphuric or nitric acid, or with hydrochloric acid and alcohol.

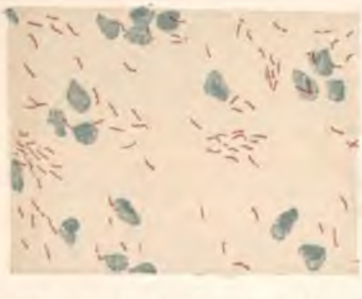


FIG. 346.—Tubercle-bacilli. Sputum of a man suffering from tuberculosis of the lung, spread in a thin layer on a cover-glass and stained with fuchsin and methylene blue. (Magnified 400 diameters.)

The decolorized preparation can then be stained with another color (Fig. 346).

The stained bacilli show not infrequently in their interior clear, glistening, unstained places, or are composed of little stained globules. Koch interpreted these clear portions formerly as spores, and this view was generally accepted for a long time. But, nevertheless, a germination of these structures cannot be proved, and at present the objects in question are no longer regarded as spores. Consequently the tubercle-bacilli produce no special resistant forms, but still the bacilli are more resistant against external influences—e.g., against drying—than are many other bacteria.

The tubercle-bacilli may be cultivated at the body-temperature and in the presence of oxygen upon solidified blood-serum, upon blood-serum gelatin, upon nutrient agar, and in bouillon; they multiply, however, very slowly, so that only on the seventh to tenth day, or even later, cultures appear at the point of inoculation in the form of dull-white flakes resembling little scales. Larger cultures form on the surface of solidified blood-serum white, irregularly shaped, dull coatings (Plate I., Fig. 4). According to Nocard, Roux, and Bischoff, the growth of the bacilli is greatly aided by the addition of from 4 to 8 per cent. of glycerin. Pawlowsky succeeded in cultivating them on potatoes in sealed glass tubes.

At temperatures below 28° C. and above 42° C. the growth of the bacilli ceases. Sunlight kills the bacilli in a short time (Koch).

If the bacilli from pure cultures are inoculated into experimental animals, tuberculosis is produced in these; and the infection succeeds as well by inoculation under the skin or in the abdominal cavity or in the anterior chamber of the eye as by inhalation of an atomized suspension of the culture and by injection of the bacilli into the veins. Guinea-pigs and cats are specially susceptible; dogs, rats, and white mice, on the contrary, are less so.

The tubercle-bacilli very likely find outside of the body of men or animals only very rarely a suitable nutrient medium for development; that is to say, they grow almost exclusively as parasites, extremely seldom as saprophytes.

The infection of human beings and of animals occurs from the taking up of the tubercle-bacilli from the lung or intestinal tract, or from wounds. Moreover, a direct transfer of the bacilli from the mother to the fœtus developing in the uterus also takes place.

In the external world the bacilli and their spores are spread mainly by the sputa, under certain conditions also by the fæces and by the urine; furthermore, from tuberculous ulcers of the skin or tuberculous organs taken from living or dead persons. Since the bacilli are tolerably resistant, they may remain preserved here, under certain conditions, for a long time, and can become mixed with the respired air as well as with the food and drink. The milk of tuberculous cows contains the bacilli, especially when the udder is diseased; it seems, however, that the bacilli may also pass over to the milk when the udder is not demonstrably diseased (Hirschberg, Ernst).

For the occurrence of an infection there seems to be required a certain *predisposition*, which lies partly in circumstances which affect the entire constitution of the individual, partly in accidental local lesions existing at the time of the infection. That tuberculosis occurs as a disease of families speaks for the former; that tuberculosis occasionally follows directly upon other morbid affections, such as tissue-lesions and inflammation, speaks for the latter; and, as further corroborative evidence, should be mentioned the circumstance that the bacilli by no means always develop on inoculation.

If the bacilli succeed in developing and multiplying in any tissue of the human body, they lead by a series of changes to the formation of *cellular nodes* or *tubercles*, which remain *devoid of blood-vessels*, and which, when they have arrived at a certain stage of development, *die out again*.

According to the investigations of Baumgarten, the first effect of the development of the bacilli in a tissue may be a hyperplasia of the fixed cells of the tissue (Fig. 347), which begins with karyomitoses (*c*, *d*) and leads to the formation of epithelial-like protoplasmic cells, which are usually designated as *epithelioid cells* (*a*). By reason of the fact that the process of cell-division repeats itself many times there are produced clumps of epithelial cells (*a*) which form little knot-like foci at the point where the bacilli multiply (Fig. 347), and at these foci the bacilli lie partly between the cells, partly in the cells themselves (Fig. 347).

Fig. 347.

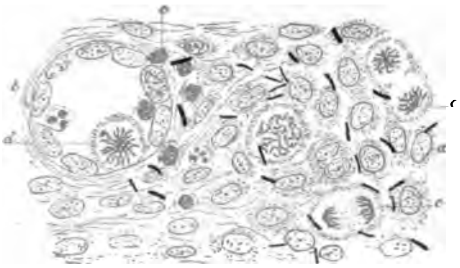


Fig. 348.

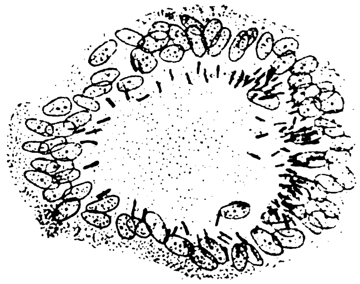


FIG. 347.—Tissue-changes produced by a recent invasion of the tubercle-bacilli. (Diagrammatic, after Baumgarten.) *a*, Hyperplastic connective tissue; *b*, Cross-section of a blood-vessel; *c*, Karyomitoses in the connective tissue; *d*, Mitoses of an endothelial cell of a vessel; *e*, Emigrated leucocytes. (Magnified 350 diameters.)

FIG. 348.—A giant cell containing bacilli with necrotic centre, from a tubercle. (Preparation stained with gentian violet and vesuvin, and mounted in Canada balsam. Magnified 350 diameters.)

By the hyperplastic development of cells the connective-tissue stroma of the original tissue is pushed more and more to one side, and even to some extent obliterated, so that the individual cells come finally to be separated from one another only by scanty fibres whose general arrangement is in the form of a net, which is consequently spoken of as the reticulum of the tubercle.

These exuberantly growing cells have for the most part one or two nuclei (Fig. 347, *a*, and Fig. 349, *b*); but usually cells containing several or many nuclei (*giant cells*) also appear (Fig. 348, Fig. 349, *a*, and Fig. 350, *c*), and these often inclose a very considerable number of large, oval, vesicular nuclei, as well as bacilli (Fig. 348 and Fig. 350, *c*).

The aggregation of large cells, when it has reached the summit of its development, may become somewhat sharply marked off from the surrounding tissue by a thick crowding together of the cells lying at the periphery.

Despite the extraordinary exuberance of cell-growth which affects the connective-tissue cells, as well as the cells of the vessel-walls lying in the morbid area and the universally present epithelial cells, a new formation of capillaries does not take place within the nodule.

Sooner or later there takes place an inflammatory alteration of the vessels (Fig. 347, *b*) lying in the diseased area, due to the presence of the multiplying bacilli, and this brings about an *emigration of colorless blood-corpuscles* (*e*).

According to observations of Baumgarten, the time at which the emigration of cells begins seems to vary according to the method of the invasion of the bacilli, and probably also according to the character of the infected tissue. It takes place earliest when the tissue is at the same time injured by any other harmful substance—e.g., by trauma. If a large-celled nodule has been formed by excessive cell-reproduction the emigration of cells leads first to an accumulation of small round cells in the periphery (Fig. 349, *c*), later to a general infiltration with round cells, which can become so extensive that the large cells may become entirely hidden. A large-celled tubercle becomes in this way a *lymphoid* or *small-celled tubercle*. If the emigration of cells takes place very early the tubercle assumes from the start the *character of a small-celled focus*. The growth of cells may fall so much behind the emigration that a large-celled nodule is not present at any stage of development of the tubercle, but constantly a *small-celled nodule*, in which the reproduction of large cells is either entirely absent or takes place only at a late stage.

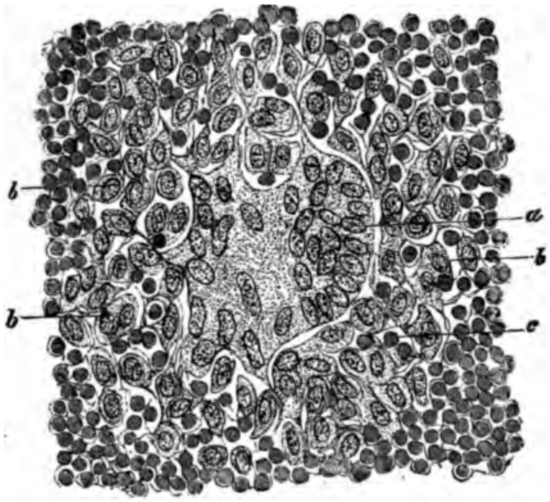


FIG. 349.—Tubercle from a fungous granulation of bone. *a*, Giant cell; *b*, Epithelioid cells; *c*, Lymphoid cells. (Preparation hardened in Müller's fluid, colored with Bismarck brown, and mounted in Canada balsam. Magnified 250 diameters.)

With the emigration of cells there is usually combined a serous exudation, and *fibrin* may be deposited in the tubercle itself as well as in the neighborhood.

The tubercle arrived at the height of its development forms a small, gray, translucent, cellular nodule which may attain the size of a millet-seed, and which incloses among its tissues more or less numerous bacilli. When it has reached a certain size *retrograde changes* usually appear in the centre, in consequence of which the cells die out. The small cells die out first; their nuclei become shrunken or break up and disintegrate. Later, the large cells also die out, become pale and homogeneous, lose their nucleus, and become glistening hyaline flakes (Fig. 350, a_1). In the giant cells at this stage may be seen not infrequently a partial necrosis, which may be recognized by a diminution in the staining power of the protoplasm (Fig. 350), an appearance which was pointed out by Weigert a few years ago. The nuclei are consequently situated more especially in that part where the protoplasm still remains alive, and they occupy sometimes a side (Fig. 350), sometimes one pole, sometimes the entire circumference of the giant cell (Fig. 348), or sometimes also the centre. The bacilli are often accumulated especially at the boundary between the dead and the living tissue (Fig. 348), but they may also lie in the portions which are devoid of nuclei (Fig. 350). Finally, the whole cellular tissue may become a uniform hyaline mass, or consist of hyaline flakes, or turn to a granular mass containing more or less abundant fat-granules. The tubercle then loses its gray, translucent character and becomes opaque and yellowish white, a change that is designated *caseation of the tubercle.*

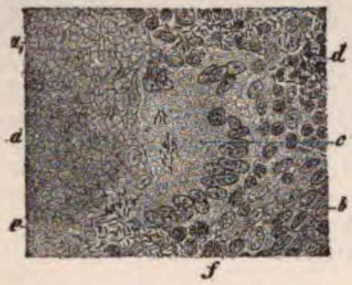


FIG. 350.—Tissue from a focus of tubercular disease, showing bacilli and a limited area of cheesy degeneration. *a*, Granular cheesy material; a_1, Cheesy material in the form of small separate aggregations; *b*, Fibrocellular tissue; *c*, Partly necrotic giant cell with bacilli; *d*, Cellular tissue invaded by bacilli; *e*, A similar invasion in tissue that is necrotic; *f*, Bacilli inclosed in cells. (Preparation treated with fuchsin and aniline blue, and mounted in Canada balsam. Magnified 200 diameters.)

If simultaneously with the tubercle-bacilli other pathogenic bacteria —e.g., pus-cocci—get into the tissues, *mixed infections* may result, which then show an anomalous behavior of the infected tissue. An invasion of pathogenic bacteria into a tissue that is already changed by tuberculosis may lead to *secondary infection.* Both occur especially in the lung.

The term tubercle (*tuberculum*) was formerly employed for all possible nodules. Baillie in 1794, and Bayle in 1810, first called attention to the gray miliary nodules which we now call tubercles. But Bayle extended the designation to other changes of the lungs. Laënnec laid the principal stress upon the caseous mass as he found it in phthisical lungs. Larger caseous nodules and lobular caseous infiltration he also designated as tuberculous. He called the nodules tubercles, the diffuse infiltration tubercular infiltration; the gray nodules—i.e., the genuine tubercles—he called *granulations miliaires.* Consequently the caseation became the chief characteristic of tuberculosis; it was designated tuberculization. Virchow pointed out, as opposed to this view, that caseous masses may result in manifold ways and therefore have very varying significance. He places the cellular tubercle as the anatomical basis of tuberculosis.

The diagnosis as to whether tuberculosis is present in a given case or not may be determined mostly without difficulty, partly on changes that are macroscopically recognizable, partly on the histological structure of the morbid area. As regards the histology of the tubercle, it may be remarked that large-celled tubercles containing giant cells are not easy to confound with anything else, whereas small-celled lymphoid tubercles are not always to be recognized immediately as such. In many organs—e.g., the lungs—tuberculous processes may spread and attain large proportions without any typical tubercles forming; so that, in order to make a diagnosis, inoculation of animals or the finding of tubercle-bacilli is necessary. Giant cells also occur in non-tubercular processes—for example, in syphilitic growths and in many tumors; but in no process are they as common as in tuberculosis, and do not usually show the peculiar grouping of the nuclei which is seen in tuberculosis. The combination of the formation of giant cells with the aggregation of epithelioid cells in nodular foci is always a sure diagnostic criterion of tuberculosis. The necrosis of the tubercles is to be regarded as a specific action of the bacilli.

The power to transfer tuberculosis from human beings to animals was established definitely by numerous experiments before the discovery of the bacilli. It was also shown by these experiments that the susceptibility of different animals varies greatly, rabbits, guinea-pigs, and ruminant animals being easy to infect, while dogs, on the contrary, are infected with difficulty. According to our common experience, the predisposition to tuberculosis is very variable within the human species itself, since only a certain number of human beings are susceptible. According to the general view, predisposition is caused by *scrofulosis* —i.e., a morbid behavior of the organism betrayed in a tendency to certain nutritive disturbances of the external skin, of the mucous membranes, of the joints, of the bones, and of the lymphatics. It is, nevertheless, to be observed that many phenomena ascribed to scrofulosis are phenomena of an already existing tubercular disease.

The onset of a tuberculous affection is usually not to be determined in human beings, since the symptoms of the disease only show themselves after the process has extended to a certain degree, consequently at a time when it is difficult to find out anything in regard to the mode of infection.

Inoculation experiments have been made in different ways. Some have inoculated under the skin, others in the abdominal cavity, or in the eye, or in one of the joints; still others made experiments in feeding tuberculous masses; others, again, introduced caseous tubercles rubbed to powder, or pulverized sputum, into the lungs with the respired air.

After the discovery of the tubercle-bacilli by Koch, pure cultures of the bacilli were often used for inoculation, and typical tuberculosis can be obtained in susceptible animals with these.

According to investigations of Koch, an active *poison, tuberculin*, can be extracted in aqueous glycerin solutions from pure cultures of the tubercle-bacilli. For obtaining large amounts of tuberculin, cultures of six or eight weeks old, in slightly alkaline veal-broth to which 1 per cent. of peptone and 4 or 5 per cent. of glycerin are added, are especially favorable. The cultures are evaporated to about one tenth the original volume by warming, and then are filtered through porcelain or siliceous-marl filters. In this way tuberculin is obtained free of bacteria, in a mixture which contains from 40 to 50 per cent. of glycerin, and thus is protected against decomposition. Tuberculin may be purified by suitable manipulation—i.e., precipitation with 60 per cent. of alcohol—and then forms a white mass which is very probably an albuminous body (Koch), but can be ranked neither with the toxalbumins nor with the peptones, since it is very resistant to high temperatures and is precipitated with acetate of iron.

According to investigations of Prudden, Hodenpyl, Vissmann, Kostenitsch, Masur, and Kockel, dead tubercle-bacilli conveyed into the tissues of an animal by inoculation, or by injection into the blood-current, or by introduction into the respiratory passages, produce, at the point of introduction, inflammation and new growth of tissue very similar to that produced by the living bacilli. When introduced in large numbers, the dead bacilli may also produce suppuration. The process, however, caused by the dead bacilli differs from that caused by the living bacilli, in the following respects: the dead bacilli become entirely destroyed in a few weeks, and the granulating nodules heal up by being changed into fibrous tissue; furthermore, the extent of the local new formation of tissue depends entirely upon the number of bacilli introduced; and, finally, no extension of the process takes place in the body. The dead bacilli contain, therefore, substances (proteins) which cause inflammation and, later, new growth of tissue.

§ 183. **Tuberculosis** at its commencement is a **local disease** that oftenest appears in the lungs, the intestinal tract, and the skin; that is to say, in places that are accessible from without. But cases often enough occur in which the first observable morbid changes appear in the tissue hidden in the depth of the parenchyma of the body—e.g., in the epididymides and testicles, in the bones and joints, in the lymphatic glands, and in the brain. So there remains no other possibility except to assume that the bacilli under certain circumstances get into the body without leaving behind a permanent change at the portal of entrance; that they develop first in distant organs to which they have been conveyed by way of the blood- or lymph-currents, and by their increase give rise to new formation of tissue and to emigration of white blood-corpuscles.

The local disease can begin with the formation of a single nodule as well as with the formation of several. In the neighborhood of these the tissue to a greater or less extent is inflamed and infiltrated with cells. In severe inflammation the formation of nodules can become indistinct or even unrecognizable, so that the primary focus of disease may present the appearance of a large granulating growth. As long as the nodules do not exceed the size of a millet-seed they are designated as **miliary tubercles.** With the further development of the process usually the

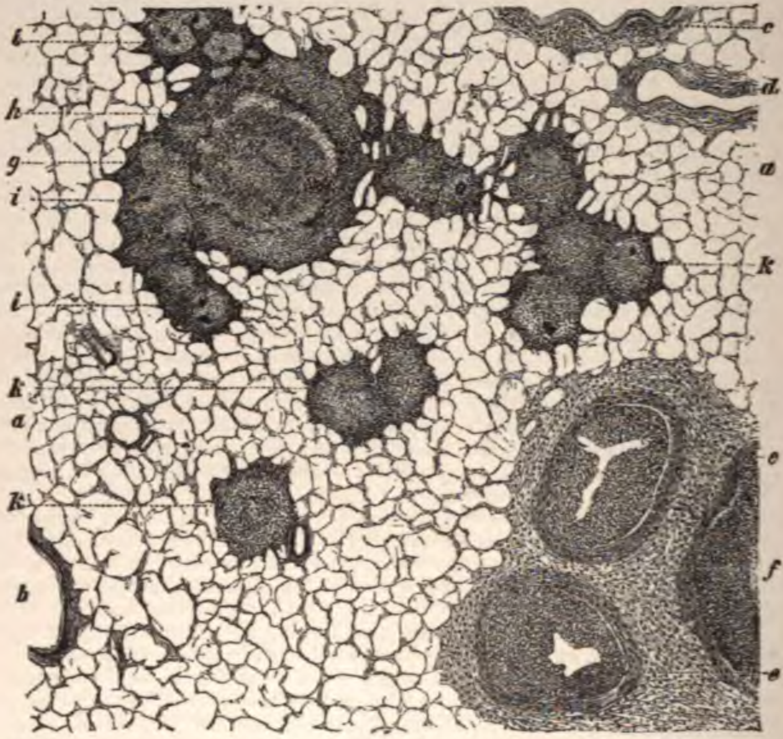


FIG. 351.—Primary tubercular nodules in the lungs, with beginning tubercular lymphangitis. Section from the apex of the left lung of a woman twenty-five years old, that contained isolated nodular foci. *a*, Normal lung-tissue; *b*, Normal bronchus; *c*, Bronchus with inflammatory infiltration of the wall; *d*, Artery; *e*, Foci of caseated bronchopneumonia encapsulated by connective tissue; *f*, Lung-tissue the seat of fibrinous induration; *g*, Caseated centre; *h*, Cellular periphery of a tuberculous focus; *i* and *k*, Miliary tubercles inside the neighboring lymph-tracts. (Preparation hardened in alcohol, colored with carmine, and mounted in Canada balsam. Magnified 15 diameters.)

next step is the formation of **large granulating nodules** (Fig. 351, *g*, *h*). That these are composed of smaller nodules can sometimes be easily recognized; but sometimes this is not clear. Caseation takes place very early in the interior of these nodules (Fig. 351, *g*), in consequence of which the nodule loses its translucent character in the centre and becomes yellowish white or pure white. Simultaneously new nodules make their appearance in the periphery of the primary focus (*i*), as well as in the surrounding tissue (Fig. 351, *k*, and Fig. 352, *i*). The latter are located in the lymph-tracts and are consequently called **miliary tubercles of the lymphatic vessels.** If inflammatory infiltration occurs between neighboring nodules the secondary nodules may become, as it were, fused with the primary nodule into one single focus of disease.

The course of local tuberculosis is usually chronic in human beings, so that weeks and months, sometimes even years, elapse before a large area of tissue is destroyed by the tubercular process. The primary granulating foci may grow in the meantime to **caseous** and **fibrinocaseous nodules** of quite considerable size before the dissemination of tubercles extends beyond the immediate neighborhood. This occurs notably in the brain (Fig. 353), where the nodules which result in this way attain the size of a hazel-nut, or even that of a pigeon's egg and larger (*c*), having a yellowish-white caseous or fibrinocaseous centre and a gray translucent periphery. In other cases calcification follows caseation; in still others the caseation may remain long absent and the new growth retain its cellular character for months and even years. This occurs notably in lymphatic glands, which thereby become converted not infrequently into large nodules consisting essentially of a tissue composed of large cells. In still other

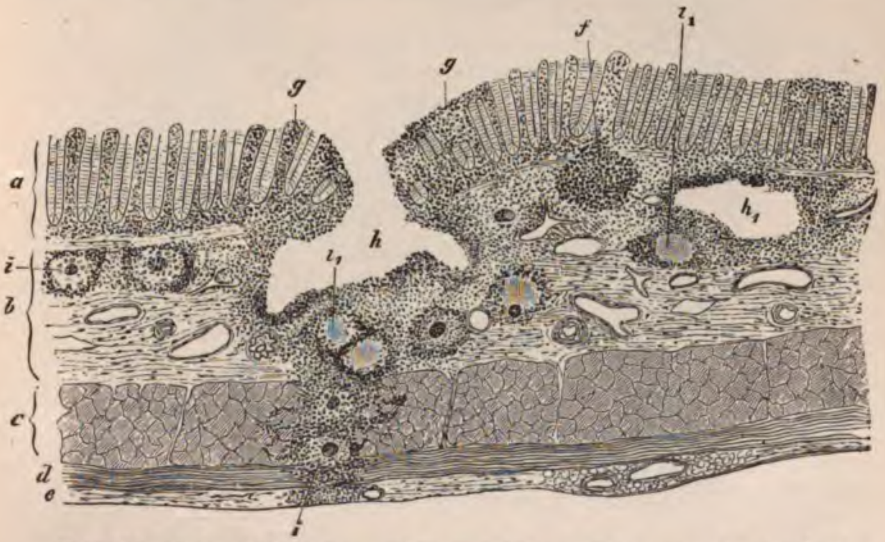


FIG. 352.—Subepithelial tubercular granulations and scattered tubercles in the wall of the large intestine. Formation of an ulcer. *a*, Mucosa; *b*, Submucosa; *c*, Muscularis interna; *d*, Muscularis externa; *e*, Serosa; *f*, Solitary follicle; *g*, Mucosa infiltrated with cells; *h*, Ulcer; h_1, Centre of softening; *i*, Fresh, i_1, cheesy tubercles. (Preparation hardened in alcohol, stained with Bismarck brown, and mounted in Canada balsam. Magnified 30 diameters.)

cases the primary tuberculous foci may become again absorbed and the tissue in the neighborhood harden into a scar. Examples occur in tuberculosis of the skin, and also of the lungs.

Most frequently, however, there will occur sooner or later, a **softening and disintegration of the caseated nodules of granulation tissue.** If these are situated in the connective tissue of the mucous membrane (Fig. 352, h_1), the softened masses break through and give rise to **ulcers** (*h*) the edges of which, as well as the surrounding tissues, are infiltrated with cells and with more or less numerous tubercles (i, i_1). The process can run a similar course, also, in the skin (Fig. 354), especially in that form of tuberculosis of the skin which is usually called **lupus.** After the breaking through of the epidermoidal cover (*g*), ulcers result here also, and in the floor, or in the margins, or the surroundings of these, small- or large-celled tubercular nodules will be found (*c*, *d*, *e*).

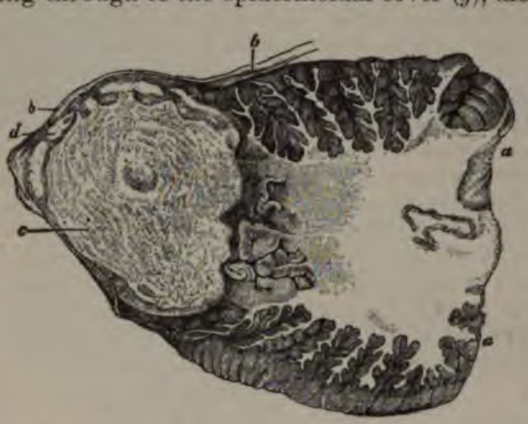


FIG. 353.—Large solitary tubercles of the pia mater cerebelli in vertical section. *a*, Cerebellum; *b*, Dura mater grown to the tubercle; *c*, Laminated tubercle; *d*, Gray peripheral zone grown to the dura mater and beset with yellowish-white nodular deposits. (Natural size.)

If caseous tubercular foci situated in the depth of the tissue disintegrate, they form in such places **hollows** or **caverns** (Fig. 355, *h*), filled

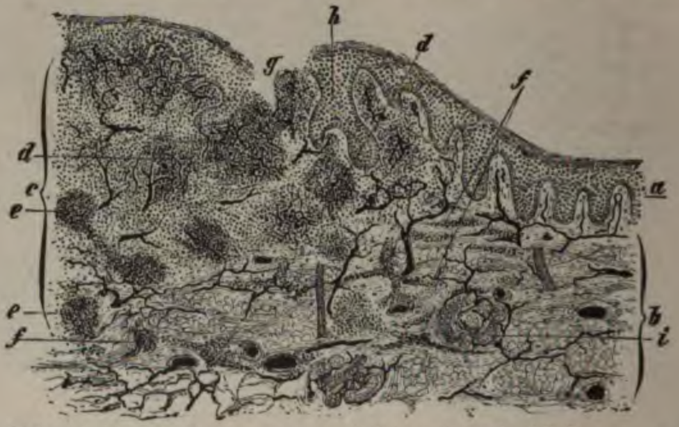


FIG. 354.—Section through a piece of skin affected with lupus. *a*, Normal epidermis; *b*, Normal corium with sweat-gland, *i*; *c*, Region of the new growth of lupus; *d*, Cellular nodules, containing blood-vessels situated within an area of diffuse cellular infiltration; *e*, Nodule without vessels; *f*, Bands of cells; *g*, Ulcer; *h*, Epithelial new growth. (Injected preparation hardened in alcohol, colored with alum carmine, and mounted in Canada balsam. Magnified 20 diameters.)

with pus and with the débris (*b*) of the disintegrated and crumbled caseous tissue, and surrounded by a tissue which is either already caseous and in the process of disintegration, or which has become changed into a granulation tissue containing tubercles (Fig. 355, *e*). The pus contained in the cavity is partly a secretion of the inflamed wall, which is consequently also called a *pyogenic membrane*.

The formation of such cavities occurs in tuberculosis of the skin, the subcutaneous tissue, the muscles and the bones, as well as in tubercular disease of the kidney, the lung, the lymph-glands, and the brain. They are oftenest, however, observed in the lungs, and may reach in this situation a considerable size. If several of these cavities of disintegration lie near one another they may become more or less melted together, as it were, by the disintegration of the intervening tissue, so that extensive sinuous cavities, or even entire **systems of caverns**, result.

Tuberculosis often runs for years or decades in an organ as a purely local process, without the neighboring organs, or the organs connected by the blood- or the lymph-stream with the diseased one, becoming affected. Thus, for example, the skin-tuberculosis called lupus may be borne for tens of years without destroying the general health and without other organs becoming infected. In the same way tuberculosis of one epididymis, of one testicle, or of one lung or one lymph-gland may also

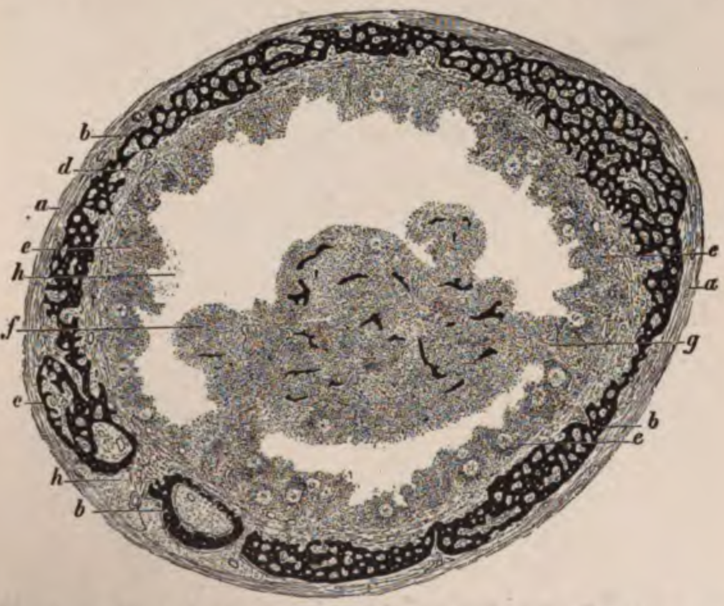
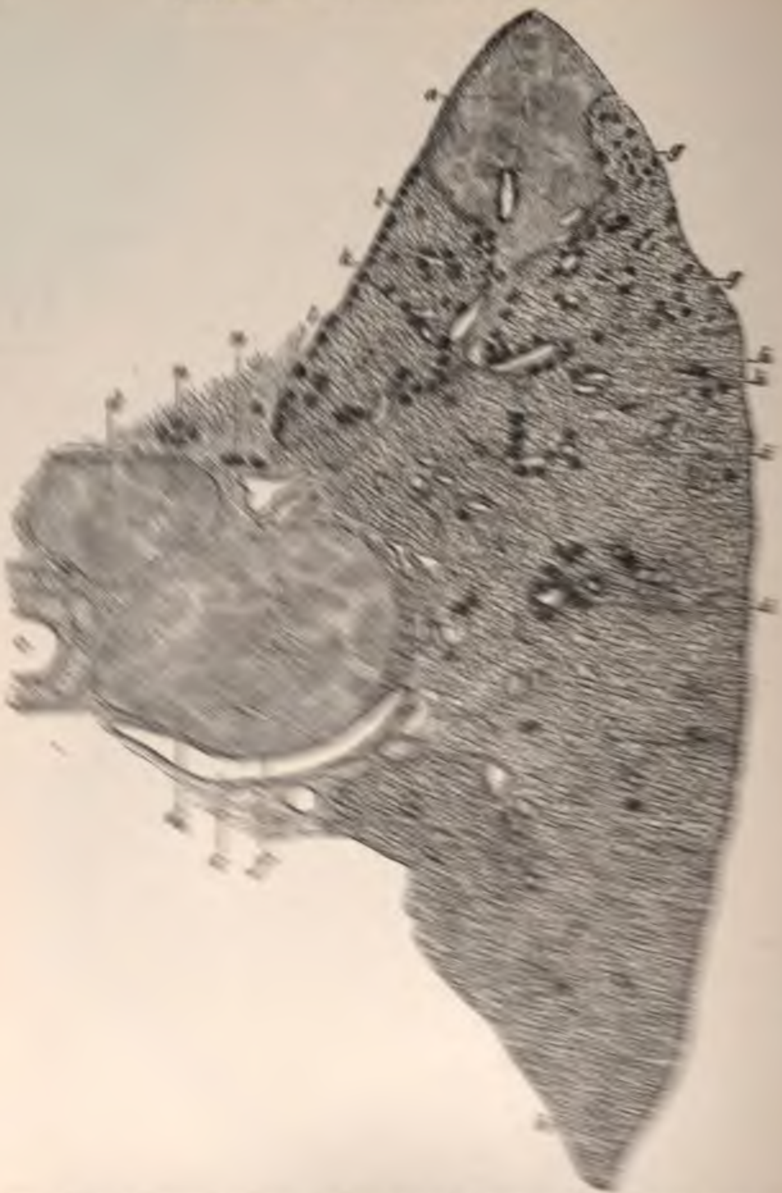


FIG. 355.—Tubercle of the centre of a bone in an advanced stage. Section through the lower part of the diaphysis of the tibia. *a*, Periosteum; *b*, Rarefied cortex; *c*, Periosteal bone-deposit; *d*, Fibrous tissue on the inner surface of the cortex; *e*, Granulation tissue containing tubercles; *f*, Sequestrum with scanty bone-scaffolding, permeated with granulations; *g*, Union of the granulations with the sequestrum; *h*, Cavity that was filled with pus and caseous material. (Preparation hardened in alcohol, decalcified with picric acid, colored with hæmatoxylin and carmine, and mounted in Canada balsam. Magnified 4 diameters.)



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remain for years confined to the organ in question. In general it can be said that the less extended the caseation and disintegration of tissue, and the greater the extension of the connective-tissue formation and the scar-formation, the more benignant the course. If a tuberculous focus is present anywhere, and if indurated connective tissue forms at this point or in its surroundings, it is apparent that the spread of the tubercle-bacilli becomes more difficult. And at the present day there is no longer any doubt that in this way tuberculous processes may be brought to **a standstill for many years** and also even **completely healed.**

It is true that such a perfect healing is not exactly frequent. Even if the tissue in the neighborhood of a caseous nodule becomes callous, even if cavities become shut off from the contiguous area by a fibrous hyperplasia of the surrounding tissue (Fig. 355, *d*), even if tubercles and groups of tubercles become walled in, as it were, by a new growth of connective tissue, still an absolutely certain protection against the further spread of the tuberculosis is not afforded. It is to be regarded as the rule that new areas will become occupied by the disease process even in cases that run the most favorable course. This **extension of the process** is characterized by the formation of new nodules, which subsequently meet with the same fate as those that formed earlier.

If the disease has started in the lung the **extension** first follows **in the lymph-channels** (Fig. 356, *g*, *h*, *i*, *k*, *l*, *m*), and in this way, after a time, without exception, the peribronchial lymph-glands (d, d_1), and frequently the visceral pleura (*l*), become involved. From the latter the costal pleura, the pericardium, and the peritoneum can become infected. If an eruption takes place of miliary nodules formed by resorption the process is called **miliary tubercular lymphangitis** (Fig. 356).

If ulcerative processes occur in the lung which in any way become connected with a bronchus, the bacilli get into the bronchial tree, and later into the windpipe, larynx, and mouth, with the expectorated sputa. From the latter they may be swallowed and then be taken up at some point in the intestinal tract.

In the *infected lymph-glands*, at the place where the bacteria settle and multiply, large-celled nodules are formed (Fig. 357, *a*), which frequently also contain giant cells (*c*) and at a later stage become caseated in the centre (a_1); or a more diffuse large-celled hyper-

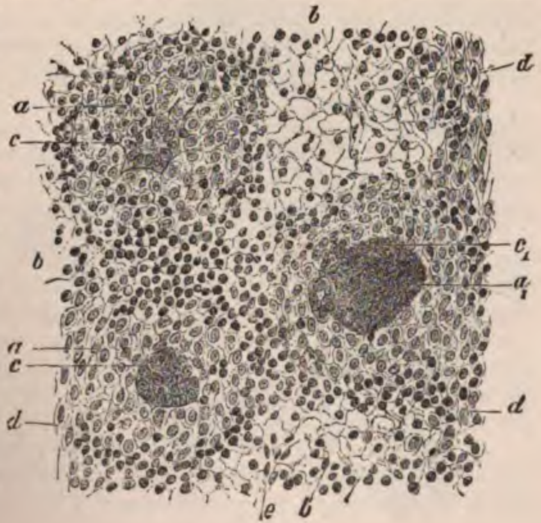

FIG. 357.—Tubercular eruption in a lymph-gland. *a*, Tubercle; a_1, Caseated tubercle; *b*, Lymphatic-gland tissue; *c*, Giant cell in the centre of a tubercle; c_1, Giant cell on the edge of an area of caseation; *d*, Large-celled tissue between the tubercles; *e*, Blood-vessel. (Hæmatoxylin preparation. Magnified 150 diameters.)

plasia may be produced by a melting together of the nodules, the caseation in the latter case taking place later. Occasionally, however, the caseation follows closely upon the new growth, so that the enlarged lymph-glands are nearly or quite caseated.

In the *infection of the serous membranes* local (Fig. 358, *a*, *b*, *c*) as well as diffuse (*d*) hyperplasia of the epithelium and connective-tissue cells appears, the former leading to the development of cellular nodules. Associated with the hyperplasia is an inflammatory emigration of cells (*e*) out of the blood-vessels; frequently, also, there is a serous or serofibrinous or blood-stained exudate in the cavities of the body. If the affected individual does not die there results a new formation of connective tissue on the surface of the serous membranes, which consequently become thickened and in many places form adhesions to the walls lying opposite. The imprisonment of gray tubercles and caseous nodules at such spots discloses later the tuberculous nature of the disease.

Of the *various mucous membranes already mentioned that are susceptible to the disease* the most usually affected are those of the larynx, of the trachea, of the ileum, and of the large intestine; and every new focus of disease behaves in the manner described above for the primary foci in the mucous membrane. The *ulcers of the mucous membrane* resulting from the breaking down of the tuberculous foci may spread on the surface as well as in the depth, are mostly irregularly shaped and sinuous, and their margin and bottom, as well as their surroundings, contain tubercles. By absorption of tubercle-bacilli into the lymphatic tracts the appurtenant lymph-glands and the pericardium become infected. If the tuberculosis starts in a kidney, the pelvis and ureter, and later also the urinary bladder, become infected by the bacilli that come off from the tuberculous focus, whereby miliary tubercles, as well as extensive subepithelial granulations, and finally ulcers, are formed. In men the different parts of the genital apparatus may become infected from the bladder. Tuberculosis usually extends to the testicle from the epididymis. Tuberculosis of the mucous membrane of the uterus and tubes may lead to tuberculosis of the peritoneum; tuberculosis of a bone to infection of neighboring bones or joints, as well as of other surrounding parts, and of the corresponding lymph-glands.

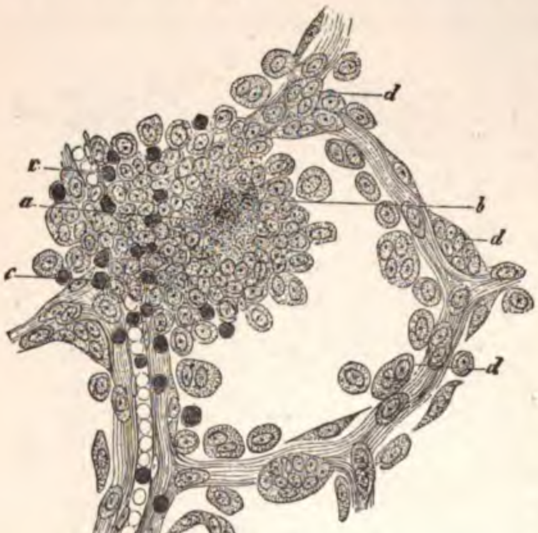

FIG. 358.—Tuberculosis omenti. *a*, Centre of a tubercle; *b*, Cells of an epithelioid character; *c*, Lymphatic elements; *d*, Hyperplastic epithelium in the neighborhood. (Preparation hardened in Müller's fluid, stained with carmine, and mounted in Canada balsam. Magnified 200 diameters)

If tuberculosis progresses in the interior of an organ, or if softening occurs in tuberculous foci, there is a constant danger of a **breaking through of the bacilli into the blood-current.** This can happen by transportation of the bacilli from caseous lymphatic glands, by way of the lymphatic vessels, into the thoracic duct, and thence into the venous system of vessels. Still, it more frequently happens that the bacilli gain access to the circulation through a direct rupture into a neighboring blood-vessel. This can also occur in foci situated in the parenchyma of any other tissue.

Tuberculous processes can encroach upon the veins of the lungs (Fig. 356, *e*, *f*) as well as upon the arteries of the lungs and upon the vessels of the systemic circulation. In this way it happens that the diseased and caseous lymphatic glands become adherent to the neighboring vessel-wall (*f*), and in consequence the tubercle-bacilli settle on the vessel-wall and finally get into the neighboring lumen of the vessel. Occasionally a thrombus is formed in consequence of the alteration in the vessel-wall. Diseased arteries may burst and cause *hæmorrhage*—i.e., hæmoptysis. Frequently, however, the bacilli get into the blood-stream, and their transportation in this way leads to the formation of **metastatic tubercles** (Fig. 359) in case the bacilli increase at any point where they become lodged.

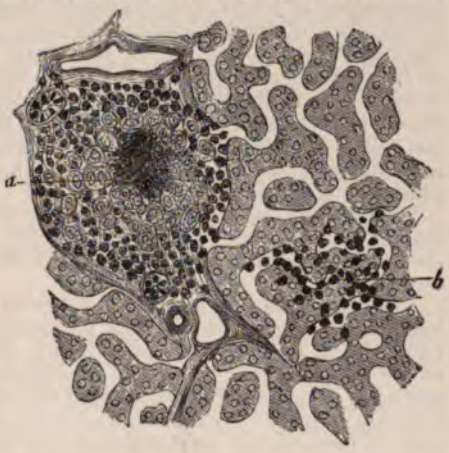

FIG. 359.—Hæmatogenic miliary tuberculosis of the liver. *a*, Fully developed tubercle in the connective tissue of the portal vein; *b*, Accumulation of round cells. (Preparation hardened in alcohol, colored with carmine, and mounted in Canada balsam. Magnified 150 diameters.)

The process of the eruption of metastatic tubercles into one or more organs is called **haematogenic miliary tuberculosis.** When the spread of tuberculosis involves the majority of the organs it is called **general miliary tuberculosis.**

The number of metastatic tubercles in an organ is, of course, very variable, and depends in the first place upon the number of bacilli that have gained an entrance into the organ. Very probably, however, the character of the tissue involved is also of importance, since the bacilli that are conveyed into an organ do not always succeed in developing. The eruption of tubercles is usually accompanied by the phenomena of inflammation, but the severity and the extent of the inflammation are very variable. The inflammation in the eruption of metastatic tuberculosis is usually most pronounced in the delicate membranes of the brain, whose cavities become occupied by a gelatinous serofibrinous or a fibrinopurulent exudate-mass. In the lung an abundant eruption of tubercles is accompanied by a high grade of hyperæmia and more or less pronounced catarrh; occasionally, also, by fibrinous exudations.

The fully developed metastatic tubercle has the same structure as the primary tubercle (Fig. 359, *a*) and those which are due to absorption by the lymph-vessels. If the individual does not die, the same processes may take their origin from a tubercle formed by metastasis as well as from a primary tubercle. If the tubercle-bacilli are swept along by the blood-stream, in the body of a woman in a state of pregnancy, *they may get into the placenta* and lead to the formation of tubercles in this situation, or *go over to the fruit*, so that in this way an **intra-uterine transfer of tuberculosis takes place from the mother to the fœtus.** It must be observed, however, that an intra-uterine tuberculosis that shows itself in the new-born takes place very rarely in this way.

A transmission of tuberculosis from the father to the embryo by the act of impregnation has not been proved, and, moreover, is very improbable.

Credit is due to Friedländer for having stated for the first time in a sharp and definite manner that there is a large number of tuberculoses which are purely of the character of a local trouble, and remain so throughout. He called attention in this connection especially to the tuberculosis of the skin called lupus, to the tuberculosis of joints, first accurately described by Virchow and Köster, to the tuberculosis of the testicle, as well as to tuberculosis of the lymphatic glands (Schüppel), which can all run for a long time as local affections. He showed, by bringing forward positive evidence, that the doctrine of tuberculosis is correct in so far as it maintains that we are not dealing with a constitutional disease that occasionally here or there evinces itself by peculiar processes of inflammation, but with a disease that arises from a noxious agent that has come from without, and that only at the place where it acts upon the tissue do the characteristic phenomena of tuberculosis appear.

Lupus had been already pronounced to be a special form of local tuberculosis, but the proof of the correctness of this view was first afforded by the detection of the tubercle-bacilli by Pfeiffer, Pagenstecher, Koch, Doutrelepont, and Demme.

In regard to the spread of tuberculosis on the surface of mucous membranes, it is worthy of note that all mucous membranes are not equally susceptible. Thus, for example, the mucous membrane of the mouth, of the throat, and of the œsophagus is much less predisposed than that of the larynx and of the trachea. Stomach, duodenum, and bile-ducts are almost immune, as is also the urethra. Since in tuberculosis we are dealing with an organized ferment, the relative immunity of the stomach, duodenum, and ductus choledochus is explained by the character of the secretions which are furnished by these parts and which hinder the development of fungi. Probably the œsophagus and urethra are favored by the fact that the substances passing over them never lie for any great length of time; whereas, in the small and large intestines, where absorption mainly takes place, the ingesta, and also with them any sputa from a tuberculous lung which may have been swallowed, remain lying for a long time. The sputa from the lung are constantly being carried over the surface of the mucous membrane of the larynx, and often remain adherent. Ureters and bladder are constantly washed by the kidney secretion. To these factors that favor a secondary infection there should probably also be added a predisposition of certain tissues.

The question as to how often tuberculosis is transmitted by transfer of the bacilli from the mother to the child, is still open. Nevertheless, according to the investigations of Schmorl, Birch-Hirschfeld, and Landouzy, in regard to miliary tuberculosis in pregnant women, it is proved that tubercle-bacilli occur in the spaces between the villi as well as in the blood of chorionic vessels, and that the liver of the fœtus may also contain bacilli. Furthermore, cases of tuberculosis of the placenta also occur which can be regarded as stages on the way of the tubercle-bacillus from the mother to the fruit (Schmorl, Kockel, Lungwitz).

Cases of tuberculosis appearing at an early period of life, reported by Demme, Baumgarten, Rilliet, Charrin, and others, speak in favor of a passage of the tubercle-bacilli from the mother to the fruit; so do also the statements of Armanni, Landouzy, and Martin, that the inoculation of portions of the organs of human fœtuses obtained from tuberculous mothers produces tuberculosis in guinea-pigs.

But still more important are the experimental investigations which de Renzi and Gärtner made; for they succeeded, by inoculation of the pregnant female in guinea-pigs, white mice, and rabbits, in producing tuberculosis in the offspring in a certain number of cases, and consequently Gärtner is of the opinion that under suitable conditions tubercle-bacilli may pass over from the mother to the fœtus in animals as well as in human beings. Finally, Maffucci and Baumgarten succeeded in effecting a transfer of tubercle-bacilli to impregnated hens' eggs, and in accomplishing this they ascertained that the infection did not disturb the development of the chicken, but, on the contrary, the bacilli that were taken up by the embryo remained in the tissue of the latter without multiplying to any considerable extent, but subsequently caused tuberculosis in the body of the chick after it was hatched out.

The experiments cited above allow the assumption that the bacilli are transferred through the placenta from the mother to the fruit, and also that they may remain for a long time in the body of the embryo without causing any recognizable changes. Since, manifestly, congenital tuberculosis in human beings is extremely rare, while, on the other hand, tuberculosis in the first years of life is frequent, it is possible that in human beings also the infection may remain latent for a long time and not be always recognized by anatomical examination. Nevertheless, it must be kept in view, according to the investigations which have thus far been made, that tuberculosis is to be referred mostly to extra-uterine infection, and that children of tuberculous parents become so often affected with tuberculosis because, on the one hand, they are predisposed to tuberculosis, and, on the other, they are more exposed to the infection with the bacilli than are the children of healthy parents.

In animals a transference of tuberculosis to the fœtus seems occasionally to occur, according to the statement of Zippelius, Jessen, Pütz, Grothans, Malvoz, Lydtin, Brouvier, Adams, and others. Johne not only found nodules and larger consolidated areas in the lung and liver, and in various lymphatic glands of a calf fœtus, but he also established beyond a doubt the presence of the characteristic bacilli.

Some of the *suppurations* that occur in tuberculous foci are to be attributed to *mixed* or *secondary infections* with the pus-cocci; still tuberculous foci may break up into a mass which resembles ordinary pus, but yet does not contain well-preserved pus-corpuscles; instead, there are fatty and broken-up cells and granular-tissue detritus—i.e., the conditions are those of a cold abscess.

Tuberculosis of cattle is a progressively spreading production of nodules, in which, along with small nodules, larger ones, the size of a potato and even larger, may form. They are situated especially in the serous membranes (Fig. 360), where the process is called the *pearl-disease;* then they are found with the next greatest frequency in the lymph-glands, the lung, the liver, the kidneys, etc. In the serous membranes the nodules often have a stem—i.e., are pedunculated. Along with caseation, calcification occurs strikingly often.

The nodules of tuberculosis of cattle and other domestic mammalia resemble precisely in structure the tubercles of human beings, and, as Koch detected the bacilli in the former, the assumption that they are identical seems justifiable.

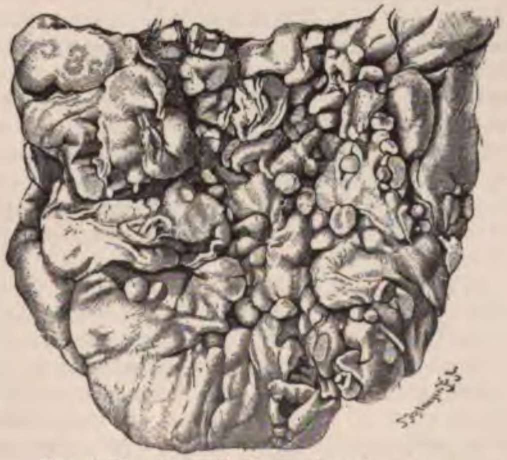

FIG. 360.—Growths from the pleura in a case of bovine tuberculosis (pearl-disease).

Experiments to determine the question of the identity of the two processes by feeding and inoculation, with a view to the possibility of transferring the pearl-disease by feeding with milk or tissues of an affected animal, have given various results. Gerlach, Orth, Bollinger, Klebs, Chauveau, Baumgarten, and others consider that a transfer occurs; Günther, Harms, Müller, Colin, Virchow, and Pütz regard this assumption as not proved. The last-named is of the opinion that neither the causal connection between tuberculosis of man and that of animals, nor the identity of the two processes, is proved.

According to Maffucci, Rivolta, Straus, and Gamaleïa, **tuberculosis of birds** is not caused by the same bacilli as tuberculosis of man or other mammalia. Cultures of the tuberculosis of man are dry, warty or scaly, and lustreless; those of bird-tuberculosis are moist, folded, and soft, and can grow even at a temperature of 43° C. Dogs are entirely immune from bird-tuberculosis, but not from tuberculosis of man. In guinea-pigs and rabbits, bird-tuberculosis does not affect the internal organs on inoculation. Chickens have immunity from tuberculosis of mammalia (Maffucci). It is still an open question whether man is susceptible to bird-tuberculosis.

According to Malassez, Pfeiffer, Eberth, Roger, Grancher, Zagari, and others, a disease very like tuberculosis occurs in guinea-pigs, rabbits, lambs, and horses, which is also characterized by the production of caseous nodules and is caused by a pleomorphic bacillus that forms zoöglœa. The affection may be called *pseudotuberculosis* (Eberth, Pfeiffer). Malassez and Vignal call it *tuberculose zoögléique.*

§ 184. At present a bacillus found by Lustgarten in syphilitic diseased foci is called the **bacillus of syphilis**, and it is possible that it has pathogenic significance and represents the *contagium of syphilis.* In favor of this, however, it can only be said that the bacilli have been found in various syphilitic foci in all stages (Doutrelepont, Matterstock); but it has not as yet been possible to cultivate these bacilli.

The bacillus resembles the tubercle-bacillus, is 3 to 7 μ long, often bent, and somewhat swollen at the ends. According to Lustgarten, it may be made visible by a complicated staining process, consisting in coloring the sections with aniline gentian-violet solution, then decolorizing them in permanganate of potassium, and washing them out in sulphurous acid. More recent authors have published other methods.

The bacilli are found in syphilitic foci of disease always in limited numbers only. They lie mostly in the cells (from one to four in a single cell) (Lustgarten), but also to some extent between the cells, and may also at times appear in the blood (Doutrelepont). The Lustgarten bacilli, at the present time, can hardly be used for differential diagnosis, since other bacilli, described as smegma-bacilli, found in the secretion from the prepuce and in the smegma between the labia majora and labia minora, stain by the method described by Lustgarten (Matterstock, Alvarez, Tavel). According, however, to Doutrelepont, Klemperer, and Lewy, it is possible to distinguish these from one another by proper staining methods—i.e., by carbolic-acid fuchsin.

The poison which on inoculation produces syphilis occurs only in the human organism, where it is alone reproduced. It is communicated to other individuals only by direct or indirect transfer. When inoculated into an organism it causes inflammatory processes of the most varied intensity and extent—from a simple, local, transitory hyperæmia to the production of large exudates or tumor-like granulations or extensive connective-tissue hyperplasias. If a child is begotten in the presence of syphilitic infection the disease may be transmitted to the child by the father as well as by the mother.

If the primary focus of inflammation is formed at the point of infection there is first a papule, which spreads over the surface and forms scales in eight or ten days after its appearance. But it may ulcerate and give rise to the secretion of a serous or purulent fluid which dries to a scab. Simultaneously the bottom becomes indurated and produces a thick disk-like deposit in the skin or a thin parchment-like thickening. Occasionally there is at first a vesicle that becomes eroded, and then an ulcer that throws off but little exudate, but which is indurated at the bottom. In still other cases there exists first an ulcer, and the bottom becomes indurated subsequently.

The induration is called the **initial sclerosis**, or *Hunter's induration.* The ulcer is called a *hard chancre.* The induration is caused mainly by an accumulation of small *round cells* (Fig. 361, *a*) in the interstices of the connective tissue. Occasionally *epithelioid cells* are formed (*b*) and *isolated giant cells* (*c*). When this takes place the summit of development is reached; then the greater part of the tissue disintegrates and ulcerates or becomes absorbed. Some of the cells are used in the formation of scar-tissue.

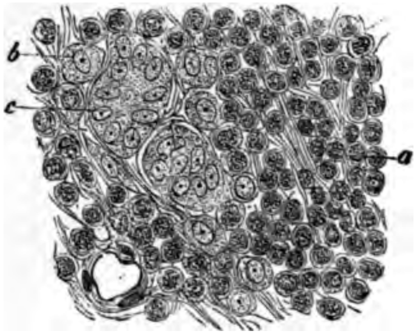

FIG. 361.—Section from a syphilitic initial necrosis. *a*, Round-cell infiltration; *b*, Large mononuclear connective-tissue cells; *c*, Polynuclear cells. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 350 diameters.)

Following upon the initial sclerosis, after a certain time, are inflammations of the lymphatic glands, of the skin, and of the mucous membranes; these are secondary symptoms. Still later, there follow syphilitic inflammations of the intestines and of the bones; these are tertiary forms of the disease. These forms sometimes resemble other non-syphilitic inflammations, and sometimes special forms of granulation are produced. Syphilitic affections of the skin embraced under the term *syphilides,* form sometimes only red blotches, sometimes small or large papillary excrescences, which may become associated with the formation of vesicles and pustules as well as with the formation of scales. Accordingly the various cutaneous syphilides have been called by different names, some of which are the following: *roseola syphilitica, papular, vesicular,* and *pustular syphilides,* and *psoriasis syphilitica* (cf. The Pathological Anatomy of the Skin). A common element in all of these affections is a more or less high degree of inflammation, which is characterized by an infiltration of the tissues, partly, also, by hyperplasia. In pustular syphilides the inflammation leads to purulent melting of the epithelium, and also, often, of the papillary body, so that ulcers result. These superficial affections reach the highest development in the *large papulous syphilide,* or the *condyloma latum* (Fig. 362), which forms, in the skin and mucous membranes, prominences flattened on top.

The change in the corium consists in extensive swelling, due to infiltration of the superficial layers, especially of the papillary body, with cells and fluid exudates. The cutis appears to be converted into a somewhat loose, gelatinous tissue rich in round cells and permeated with fluid (Fig. 362, *i* and *k*). Usually the granulation tissue formed is not fully developed, for the organization of the cellular material is lacking, as well as the necessary new formation of vessels. It is only in condylomata of the mucous membranes that the tissue becomes like granulation tissue by its richness in cells. The epithelium is swollen and turgid, and permeated by fluid and cellular exudate (Fig. 362, *d*, *e*, *f*, *g*).

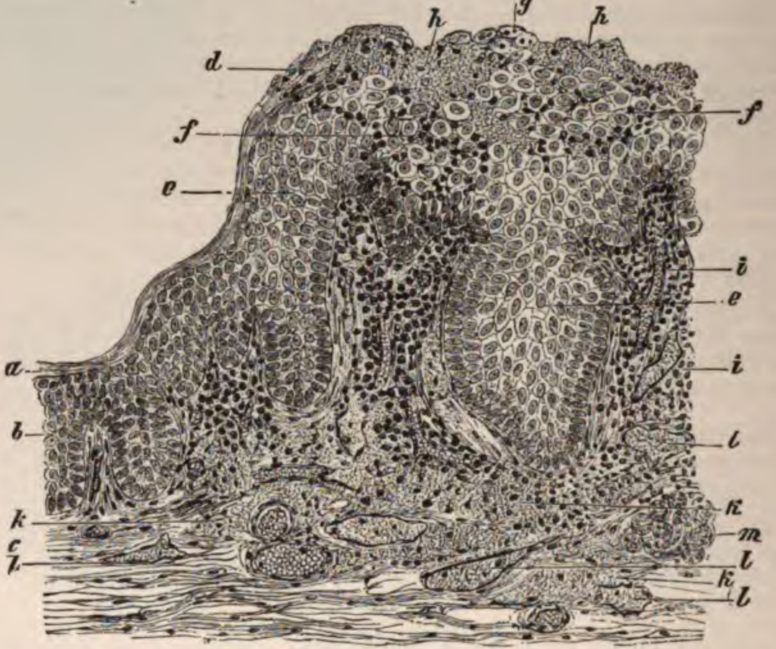

FIG. 362.—Condyloma latum ani. *a*, Horny layer; *b*, Mucous layer of the epidermis; *c*, Corium; *d*, Loosened horny layer infiltrated with small cells; *e*, Swollen mucous layer; *f*, Swollen and infiltrated mucous layer; *g*, Epithelial cells with round cells inside; *h*, Coagulated granular masses; *i*, Swollen papillary body infiltrated with cells and fluid; *k*, Corium infiltrated with cells, fluid, and coagulated albumin; *l*, Widened lymph-vessel filled with coagulum; *m*, Sweat-gland. (Preparation hardened in alcohol, colored with Bismarck brown, and mounted in Canada balsam. Magnified 150 diameters.)

Syphilitic lesions that appear in internal organs, in lymphatic glands, in bones, in muscles, in subcutaneous and submucous connective tissue, in the membranes of the brain, etc., constitute formations that are usually designated as **gummata** (Virchow), except where they consist merely of a light grade of a degenerative or an inflammatory change, without characteristic features. In its earlier stages a gumma, as well as the broad condyloma, consists of an inflammation confined to one kind of tissue. But usually the gumma is richer in cells and attains a higher degree of development, as shown by the fact that a peculiar granulation tissue with new blood-vessels (Fig. 363) is formed. The gumma occurs especially in the periosteum, in the membranes of the brain, as well as in the parenchymatous organs of the abdomen, especially in the liver, the spleen, and the testicle, and shows a difference in the abundance of cells according to location. The forms which have a paucity of cells, and which are most often observed in the bones, have a soft consistence and present a gelatinous appearance on section, owing to the fact that the fluid portion of the node is in excess of the cellular mass. The tissue also undergoes a partial metamorphosis into mucous tissue. Forms rich in cells are met with especially in the soft membranes of the brain (Fig. 363), in the submucosa of various mucous membranes, in the liver, in the testicle, and in the spleen. They form gray or grayish-white or grayish-red foci, sometimes spherical, as in the spleen and testicle, sometimes more irregularly shaped, as in the soft membranes of the brain; and in their light-gray or reddish-gray color, and somewhat transparent texture, they resemble healthy *granulations*. Often, besides these lesions, diffuse inflammatory changes are also present in the affected organs.

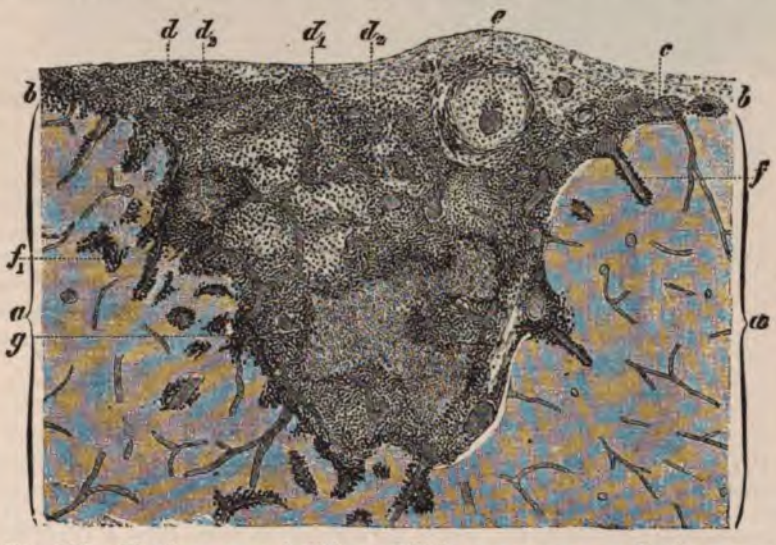

FIG. 363.—Meningo-encephalitis syphilitica gummosa. *a*, Brain-cortex; *b*, Pia mater; *c*, A vein surrounded by cellular exudate; *d*, Fresh cellular granulation tissue; d_1, Fibro-cellular granulation tissue; d_2, Caseated granulation tissue; *e*, Artery with much thickened intima and adventitia infiltrated with cells; *f*, Cellular infiltration of the pia-sheath of the cortical vessels; f_1, Perivascular cellular infiltration of the cortical substance; *g*, Diffusely spreading cellular infiltration invading the brain-cortex. (Preparation hardened in Müller's fluid and alcohol, colored with alum carmine, and mounted in Canada balsam. Magnified 15 diameters.)

Small foci of syphilitic infiltration quite often disappear quickly by absorption. In larger foci frequently suppuration or fatty and necrotic disintegration takes place. Disintegration of syphilitic foci of the skin and of the subcutaneous connective tissue, as well as of the mucosa and submucosa, leads to the formation of **ulcers**, which, when a mucous membrane is the part affected, occur most frequently in the region of the mouth, throat, and upper air-passages (Fig. 365, *a*). In the interior of deeper-lying gumma-nodules caseous foci are not infrequently formed (Fig. 363,

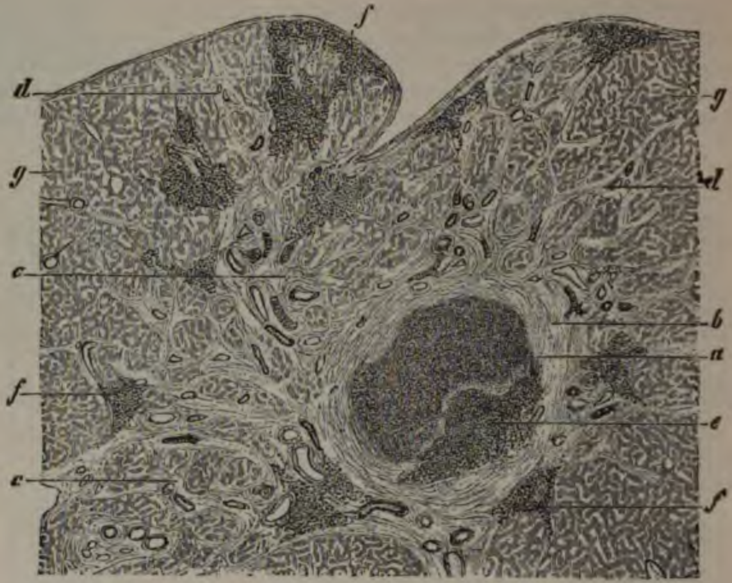

FIG. 364.—Gumma of the liver. *a*, Caseous nodule; *b*, Homogeneous connective tissue; *c*, Connective tissue with remnants of liver-tissue; *d*, Connective-tissue bands radiating into the liver-tissue; *e*, Cellular foci at the edge of the caseous nodule; *f*, Cellular foci within the connective-tissue rays; *g*, Liver-tissue. (Preparation hardened in alcohol, colored with alum carmine, and mounted in Canada balsam. Magnified 12 diameters.)

d_2, and Fig. 364, *a*). These are sometimes regularly spherical, sometimes irregularly shaped. The peripheral portions merge into callous connective tissue (Fig. 362, *b*, *c*, *d*) which incloses the caseous masses and radiates in bands into the surrounding tissue. *Papillary growths* (Fig. 365, *b*, *c*) not infrequently are formed in the neighborhood of the ulcers of the mucous membrane.

Necrotic remains of gumma-nodules which originally were cellular come under anatomical examination far more frequently than those which are still perfect; and yet in this changed condition they are still commonly designated as gumma-nodules. Not only the cellular hyperplasia, but also the infiltrated tissue itself, is often involved in these necrotic changes.

The reason why syphilitic inflammation often results in disintegration of tissue and necrosis lies primarily in the character of the agent that produces the disease. Still a second circumstance is responsible for this manner of termination—namely, the extensive participation of the blood-vessels, especially of the arteries, in the inflammation. Where a syphilitic inflammation leads to a formation of granulations or to a connective-tissue hyperplasia the vessel-walls also become thickened, especially the intima (Fig. 363, *e*), so that the lumen of the vessel becomes narrowed and not infrequently even totally closed. Occasionally the syphilitic process is largely localized in the vessels.

Hereditary syphilis is characterized mostly by peculiar tissue changes which differ not inconsiderably from the manifestations of acquired syphilis; but still changes also occur which agree with the latter. In the skin it causes maculose as well as papular and pustular syphilides, which may lead to ulcerations. The spleen is usually more or less enlarged, and in individual cases may attain ten times its normal volume. In the liver intra- as well as perivascular aggregations of round cells are formed, and these often group themselves in small, thick foci. There are also cases where there is a diffuse, wide-spread hyperplasia of the connective tissue, which lends a solid character and a peculiar brownish-yellow color to the liver. Moreover, in some cases there is a connective-tissue hyperplasia confined to the periportal tissue. The lung may present, throughout its substance or only in places, a thick gray or grayish-white character resembling sarcomatous tissue. This appearance in the altered area is due to the presence of connective tissue rich in cells (Fig. 366, *a*, *b*), containing only imperfectly developed alveoli (*e*, e_1) and bronchi (*d*, d_1), or none at all. In dis-

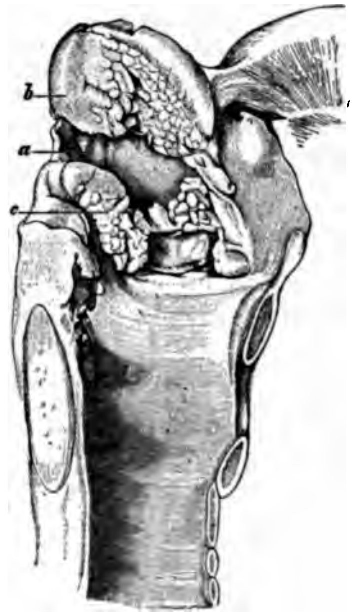

Fig. 365.—Extensive syphilitic ulceration of the larynx. Sagittal section through the larynx and trachea. *a*, Ulcer; *b*, Thickening and papillary growth on the epiglottis; *c*, Thickening and papillary growths of the left wall of the larynx and of the superior thyro-arytenoid ligament. (Natural size.)

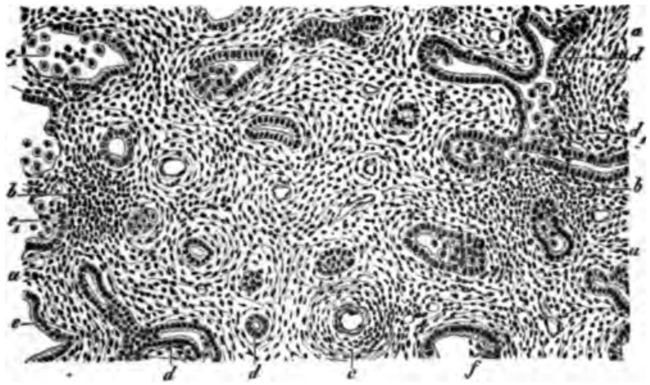

Fig. 366.—Changes in the lung in congenital syphilis. *a*, Hyperplastic stroma rich in cells; *b*, Foci of granulations rich in cells; *c*, Arteries with thickened adventitia; *d*, d_1, Gland-like bronchi, some of which contain desquamated epithelium and round cells; *e*, e_1, Alveoli, some of which, e_1, contain desquamated epithelium and round cells. (Preparation hardened in Müller's fluid, colored with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 40 diameters.)

ease of limited extent there exists only a thickening of the peribronchial and perivascular tissue and of the interalveolar septa, in part associated with an accumulation of desquamated epithelial cells in the alveoli. In the kidneys and testicles the connective tissue may also be increased in places and enormously rich in cells. Syphilis thus often causes in glandular organs a *pathological development of the connective-tissue elements*, while the epithelial tissue remains behind in its development. In the blood the number of colorless corpuscles often seems increased (Stroebe). Finally, in the bones, not infrequently *disturbances in the endochondral ossification* occur—disturbances which are characterized mainly by irregularities in the formation of the medullary cavity, and in the deposition of lime-salts in the cartilage, and which lead to disturbances in the structure of the spongy subchondral bone-substance. By the formation of hyperplastic granulations which undergo caseous degeneration, larger defects may occur in the bone-tissue.

Syphilis can be transferred to the fœtus as well by the sperm as by the ovum. The transmission from the father's side is the most usual. After conception, a transfer of syphilis from the mother to the fœtus may take place. Most frequently the transfer of syphilis occurs in the secondary stage. If infection and conception occur simultaneously, the intensity of the disease in the child is greatest; but, nevertheless, even freshly infected parents may produce healthy children (Neumann). The syphilis that is transferred by the mother during the first months of pregnancy kills the child. In the later months of pregnancy, syphilis, as a rule, is not transferred to the child (Neumann).

Mothers that bear children which have been infected with syphilis by the father may themselves remain healthy. It appears, therefore, that a certain immunity from syphilis does occur.

§ 185. The **Bacillus lepræ** was first described by Armauer Hansen in 1880. It is a small, slender bacillus, from 4 to 6 μ long. It is regarded as the cause of **leprosy**—also called *elephantiasis Græcorum*. It is found constantly and in large numbers in the morbidly altered tissues (Figs. 367, 368, and 369).

The foci of disease in leprosy are characterized in general by a hyperplasia consisting of cells of different size, and of fibrous stroma (Fig. 367). The bacilli lie partly between (*e*), partly in the cells (*c*, *d*), and accumulate

Fig. 367.

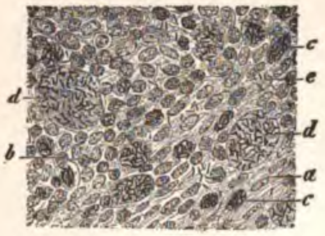

Fig. 368.

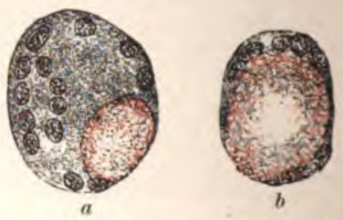

FIG. 367.—Tissue from a leprosy-nodule. *a*, Cellular fibrous tissue; *b*, Round cells; *c*, *d*, Medium- and very large-sized cells filled with bacilli; *e*, Free bacilli. (Preparation treated with fuchsin and methylene blue. Magnified 200 diameters.)

FIG. 368.—Two giant cells with vacuoles containing bacilli, from a leprous growth of the skin of the nose. (Hardened in alcohol, stained by Gabbet's method, and mounted in Canada balsam. Magnified 400 diameters.)

usually to a large extent in the latter. The cells, in consequence, swell enormously (*d*), and change into giant cells of one or more nuclei (Fig. 368). The giant cells occasionally inclose large vacuoles which contain large numbers of bacilli, as well as granular, thready detritus of the liquefied protoplasm. The nuclei are preserved for a certain time, and are shoved over to the periphery by the vacuoles containing the bacilli. Later on, they too are destroyed, so that the entire cell then becomes a vesicle containing the bacilli (Fig. 367, *d*). Some of the cells in which the bacilli lie are tissue-cells which were present before the invasion, while others are newly formed cells.

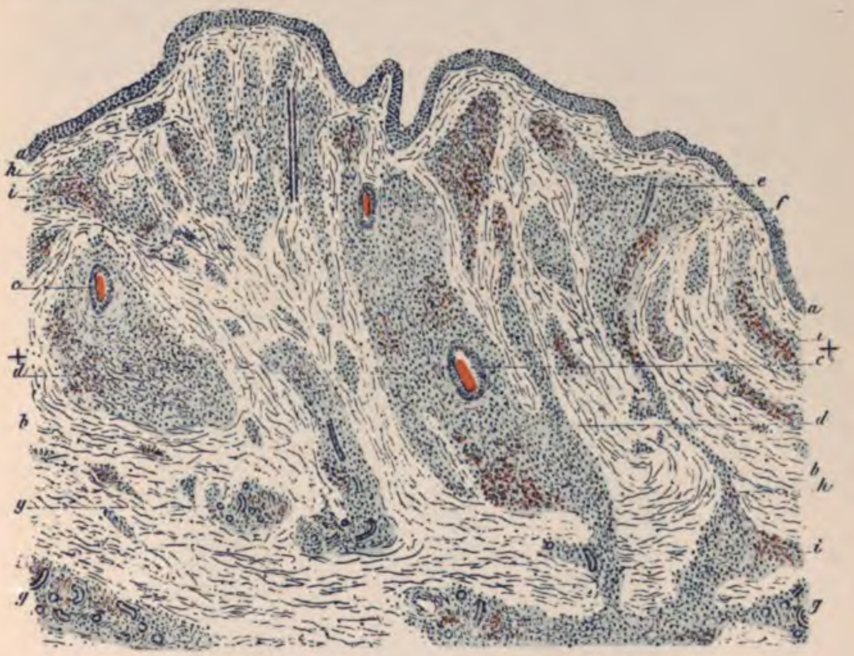

FIG. 369.—Section through a leprous skin-nodule. *a*, Epidermis; *b*, Corium; *c*, Hair-follicle; *d*, Leprous foci in the tissue surrounding the hair-follicles; *e*, Duct of a sweat-gland; *f*, Leprous foci in the neighborhood of *e*; *g*, Leprous foci around the sweat-glands; *h*, Leprosy-nodules in which no special connection with any elements of the skin can be recognized; *i*, Foci of bacilli. (Preparation hardened in alcohol, treated with fuchsin and methylene blue, and mounted in Canada balsam. Magnified 32 diameters.)

The bacilli are surrounded by a slimy envelope (Neisser), and behave toward coloring-matters in much the same manner as do the tubercle-bacilli. Consequently the same procedure can be used for staining the former as the latter. In order to make them distinctly visible in tissues, and at the same time to enable the observer to recognize the structure of the diseased tissue, the best plan is to stain the sections in a solution of fuchsin in aniline water, and, after decolorization in acid, to treat them with methylene blue (Figs. 368 and 369). The stained bacilli often show clear spots, or appear as if made up of stained granules.

According to Bordoni-Uffreduzzi and Neisser, the bacilli may be cultivated upon peptone-glycerin-blood-serum, upon gelatinized blood-serum, and upon boiled eggs. They grow out to threads of four times the original length, and are often swollen into club shape on the ends. It is still a contested point whether the bacilli form spores.

Inoculations of animals have as yet not given certainly positive results. It is true that it is claimed that the bacilli can multiply at the seat of inoculation, and that a hyperplasia may take place in rabbits (Damsch, Vossius); still a disease process extending over large areas of the body is not obtained. Schottelius and Bäumler obtained no positive results by inoculating apes with freshly excised pieces of leprous skin rubbed up so as to form an emulsion in warm bouillon and warm blood-serum. According to Campana and Wesener, the bacilli in the pieces that are inoculated are carried off by the wandering cells, but they cause no specific infection and do not multiply.

It is still a disputed matter whether the infection in man takes place by mediate or by immediate transference from individual to individual (Neisser), or whether the bacilli develop as a miasm outside the body (Hirsch). In regard to inheritance, authors are also of different opinions. Hirsch holds that inheritance is certain; Neisser and Hansen, on the contrary, declare it to be very improbable. The presumption is that after the entrance of the bacilli into the body a long time elapses before the first

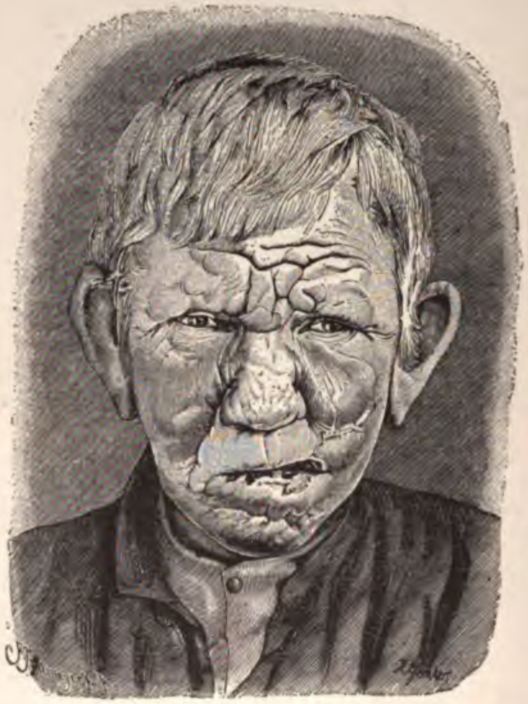

FIG. 370.—Leontiasis leprosa. (After G. Münch.)

symptoms appear. In spreading in the body they make use mainly of the lymph-channels; they may, however, get into the blood.

The skin and the peripheral nerves are mainly concerned in the disease; still the bacilli can multiply in other tissues—e.g., in the testicles, in the liver, in the ganglia, and in the spleen—and form foci of disease.

At the point of colonization the bacilli excite inflammation and hyperplasia. Granulation tissue containing blood-vessels is formed, and remains for a long time in a condition which is characterized by an abundance of cells. This forms the basis for nodules and tumors in the skin and for spindle-shaped thickening of the nerves, and is the cause of the irritation and eventually of the degeneration and destruction of nerve-filaments. The bacilli, and the hyperplasia of the tissues caused by them, group themselves by preference around the hair-follicles (Fig. 369, *d*) and the ducts (*f*) and coils (*g*) of the sweat-glands; but this connection is not always to be made out in all of the hyperplastic foci (*h*). The bacilli may furthermore penetrate into the blood-vessels, the hair-follicles, and the sweat-glands (Touton), and thence come to the surface. In the nervous system they are found in the connective tissue as well as in the nerve-elements themselves, especially in the ganglion-cells (Sudakewitsch). The cells occupied by them undergo, in time, degeneration, occasionally with hydropic swelling and the formation of vacuoles (Fig. 368).

The hyperplasia caused by the growth of the bacilli may almost disappear by disintegration and absorption of the cells after the condition has existed for years; but there always remain induration and pigmentation of the skin. Caseation never takes place.

Leprosy of the skin appears especially in the face, on the extensor surface of the knees and of the elbows, and on the posterior surface of the hands and feet. It begins by the formation of red spots, that either disappear, leaving pigmented spots behind, or become elevated into nodules of brown-red color—*lepra tuberosa* sive *tuberculosa* sive *nodosa*. In the region of the red spots the tissue contains large numbers of bacilli (Philippson), which for the most part lie within the vessels, and already at this stage the tissue-hyperplasia can be detected. According to investigations of Müller, the vesicular eruptions that occur in leprosy, and were formerly regarded as a sequel of a leprous disease of the nerves, are caused by the presence of bacilli.

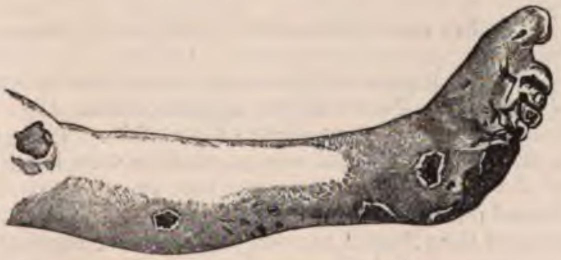

FIG. 371.—Lepra anæsthetica ulcerosa of the lower extremity and foot. (After G. Münch.)

The nodules remain for months unaltered, or they increase in size and become fused together into a single mass, so that very large tumors result,

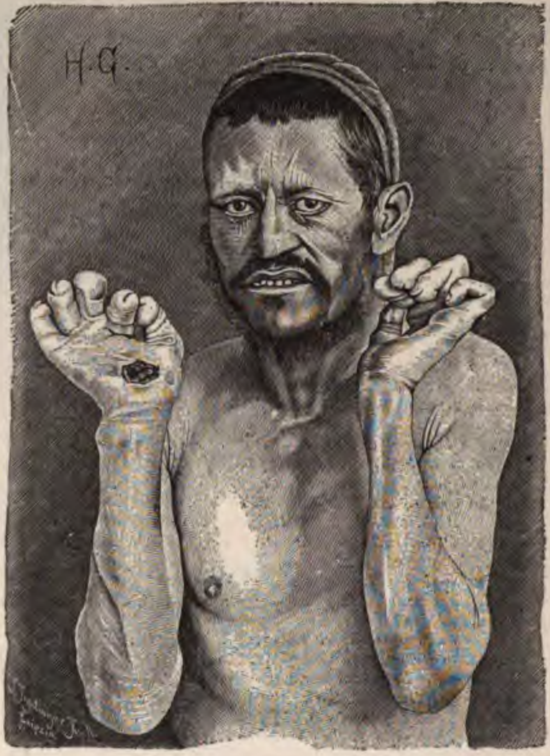

FIG. 372.—Lepra anæsthetica mutilans. Partial destruction of the fingers; ulcers in the hand. (After G. Münch.)

which have led to the name *facies leontina* (Fig. 370) being given to the distorted face.

The formation of ulcers which show no disposition to heal may result from *external influences.* New nodules appear occasionally, following an erysipelas-like reddening and swelling of the skin. The glands of the submaxillary and of the inguinal region swell to very large nodules.

Leprosy of the nerves (*lepra nervorum* sive *anæsthetica*) leads first to hyperæsthesia and pain, later to anæsthesia, more seldom to motor paralysis in the region of the affected nerves. The further consequences of the disease of the nerves are disturbances that show themselves in the skin in the form of white and brown spots (i.e., *lepra maculosa, morphæa nigra et alba*), and in the bones and muscles by atrophy. Since those suffering from the disease frequently injure themselves after the appearance of anæsthesia, ulcers are often formed which cause deep erosions and may lead to the loss of entire phalanges (*lepra mutilans*) (Figs. 371 and 372).

Leprosy of the skin and leprosy of the nerves occur usually in combination, seldom separately. Along with the skin and the nerves, the central nervous system, the mucous membranes, the cornea, the cartilage, the liver, the spleen(Virchow), the lymphatic glands, and the testicles may all become affected.

In Europe leprosy is confined mainly to Norway, Sweden, Finland, the

Baltic Sea provinces of Russia, and the coast of the Mediterranean Sea. It occurs very frequently in Hindustan, China, Sumatra, Borneo, Java, and Mexico, on the northern and eastern coasts of South America, in Upper and Lower Guinea, in Cape Colony, and on the northern coast of Asia.

§ 186. The **Bacillus mallei** is a bacillus discovered by Löffler, Schuetz, and Israel in glanders foci. Subsequently the observation was substantiated and the bacillus studied by Weichselbaum, Kitt, and others. It is to be regarded as the **cause of glanders** and of **farcy** (*malleus, maliasmus*), a contagious disease of horses, which occurs in man only by transference from horses.

The glanders-bacilli are very small, slender bacilli, which occur in the foci of disease sometimes scattered, sometimes lying together in little clumps. For staining, alkaline methylene blue or gentian violet is usually employed.

The stained bacilli often show clear spots that are regarded by many as spores, but are interpreted by Löffler as forms of involution. They occur especially in the glanders foci, but occasionally also in the blood of the diseased individual (Löffler, Kitt).

The bacilli grow at temperatures varying from 30 to 40° C. on coagulated blood-serum, as well as on slices of boiled potato and on potato-pap. On the two latter they form amber-yellow coatings that later become red. On blood serum they form small, yellowish, transparent droplets which later become milky white. On agar-agar the colonies are grayish white. Whether the bacilli form spores or not, is not yet determined.

Dried bacilli die usually in a few weeks. Cultures are sterilized by being once actually boiled, as well as by heating at 55° C. for ten minutes (Löffler). Sublimate in a solution of 1 : 5000 kills the glanders-bacilli certainly in two minutes.

Horses, asses, sheep, young dogs, goats, cats, guinea-pigs, and field-mice are suitable for inoculation. Field-mice, when subjected to subcutaneous inoculation, die in eight days, and then show the spleen or the liver filled with small cellular nodules containing bacilli (Flügge). In guinea-pigs there results an ulcer at the seat of inoculation, and at the same time there is swelling of the neighboring lymph-glands. At a later stage nodules as well as nasal ulcers may be formed in the internal organs. In horses and asses typical glanders can be produced. Cattle, white mice, and house-mice are insusceptible.

The usual atrium of infection in horses is the mucous membrane of the nose. Then, next in order, the submaxillary glands become affected, and in the further course of the disease there are metastases in different organs. In the nasal mucous membrane, the infection may give rise either to a diffuse cellular infiltration of the mucous membrane, or, on the other hand, to subepithelial nodules the size of a millet-seed or a pea, which resemble lupus-nodules. In the chronic farcy of the skin larger nodules are developed, which join together in rows, forming worm-like cords.

The nodules of the mucous membrane break down easily. The cells of which they are composed bear precisely the character of lymphatic elements or of pus-cells. By the disintegration, softening, and suppuration of the nodules, ulcers are formed with yellow infiltrated bottoms. They enlarge by a continuance of the process of nodular or more diffuse infiltration and subsequent disintegration of the edge, as well as by confluence of neighboring ulcers. Horses that have died of glanders have often very extensive, irregularly shaped, elevated ulcers on the mucous membrane of the vomer. These ulcers have eroded edges and floors which are coated with a gray and yellow material; and besides these there are numerous small lenticular ulcerations and gray or yellow nodular foci which are on the point of breaking down. The whole process stands very nearly related to purulent inflammation. The healing of the ulcers is characterized by the formation of radiating scars.

The lymphatic glands are constantly the seat of inflammatory swelling. Of the internal organs the lungs particularly are affected. They either contain nodules which present, on section, a cheesy and disintegrated centre, while the periphery is grayish in color and rich in cells, or else foci of lobular pneumonia. The latter may have either a light-gray or a more hæmorrhagic appearance, or they may have already become opaque and of a yellowish white color, by reason of fatty and caseous changes. Occasionally the mucous membrane of the intestinal tract may contain nodules of varied size, some of them light gray, and consequently rich in cells, some of them of an opaque, yellowish-white color, cheesy, or on the point of suppurating.

In farcy, which has more of a chronic course than glanders, the nodules which form in the skin and muscles consist of small-celled tissue which finally undergoes a retrograde metamorphosis, becomes caseated, and disintegrates.

In human beings the infection with glanders-poison takes place mostly through small wounds of the skin; it can, however, also appear primarily on the mucous membrane at the point where it joins the skin. In the skin and subcutaneous tissue the following lesions may develop: carbuncular and phlegmonous inflammations which may result in suppuration; nodular, vesicular, and pustular exanthemata; and suppurative inflammation of the lymphatic vessels and glands. In the mucous membranes of the respiratory passages catarrhs appear, and suppurating nodules and nodes are formed, which leave ulcers behind. In the internal organs metastatic, small-celled nodules are formed, that show a tendency to suppurate or to form extensive suppurative infiltrations or abscesses, especially in the muscles. In chronic farcy occasionally large nodules are formed in the skin and muscles, and these break down and give rise to ulcers that are slow to heal.

For staining the glanders-bacilli (Löffler) the sections of tissue are placed for a few minutes in a potassium-hydrate solution of 1:10,000; then in an alkaline methylene-blue or gentian-violet solution, made by mixing 3 ccm. of a 1:10,000 solution of caustic potash and 1 ccm. of an alcoholic solution of methylene blue or gentian violet. The sections are decolorized for a few minutes in the following solution: 10 ccm. of distilled water, 2 drops of sulphurous acid, and 1 drop of a 5 per cent. solution of oxalic acid.

According to investigations of Kalning and Preusse, a potent poison, *mallein*, can be extracted from cultures of the glanders-bacillus. This substance when injected in small doses into horses suffering with glanders, causes febrile rise of temperature and may be used as a diagnostic aid (cf. Johne *).

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* "Resultate der in Sachsen vorgenommenen Mallein-Rotzimpfungen bei Pferden," *Deutsche Zeitschr. f. Thiermed.*, xix., 1893.

§ 187. Under the name of the **bacilli of rhinoscleroma**, Frisch, Pellizari, Chiari, Cornil, Alvarez, Köbner, Paltauf, von Eiselsberg, Dittrich, and others have described short rods with rounded ends (Fig. 373) which constantly occur in the morbid formation called *rhinoscleroma* or *scleroma respiratorium* (Bornhaupt, Wolkowitsch), and consequently are regarded as the cause of the disease. Staining succeeds best with methylene violet; the sections being left in the mixture for from twenty-four to forty-eight hours. After staining, the sections are treated with iodine water, or are left for from one to three days in absolute alcohol.

The bacilli possess mostly a hyaline capsule. According to Paltauf, von Eiselsberg, Dittrich, Wolkowitsch, and others, they may be cultivated on blood-serum, gelatin, agar-agar, and potatoes; and under these conditions they form capsules (Fig. 373). When cultivated in bouillon, on the contrary, they show no capsules (Dittrich). Stab-cultures in gelatin resemble very much the nail-cultures of the pneumonia-bacilli of Friedländer, but are of a transparent grayish-white color, and not dead white. The bacilli stain more readily than the pneumonia-bacilli, and also stain by Gram's method. Stepanow observed, in inoculations into the eyes of guinea-pigs, active inflammations and proliferating granulations containing the bacilli and hyaline-degenerated cells.

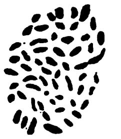

FIG. 373.—Bacillus of rhinoscleroma from an agar-agar culture three days old. (Preparation of Stepanow, stained with gentian violet, decolorized with oil of cloves and xylol, and mounted in Canada balsam. Magnified 750 diameters.)

Rhinoscleroma is observed principally in east Austria and in southwest Russia; isolated cases also occur in Silesia, Italy, Egypt, Belgium, Sweden, and Switzerland, and in South America. It is a chronic progressive disease of the tissues which lasts for many years, usually beginning in the nose (Wolkowitsch), more rarely in the throat, larynx, or palate, and extending thence to the neighboring parts—the external nose, lips, tear-passage, trachea, etc. The affection in the nose is characterized by a thickening of its walls which in some cases is diffuse, but in others is lumpy or nodular. The external skin assumes a reddish or brownish-red color, becomes stiff and cracked, and is covered with scales. In the throat and respiratory passages tough cartilaginous infiltrations are sometimes found, and at other times shrunken scar-tissue. The infiltrations may appear at times in the form of nodules or nodes, at other times in that of tumors and flat thickened areas; or, finally, they may be spread out more diffusely. By the transformation of the infiltration into shrunken scar-tissue extensive deformity of the affected organs may result. Deeply extending destruction of tissue is absent, but, on the other hand, superficial ulceration may take place. The infiltrated tissue on section appears yellowish and fatty, but not infrequently it shows a gray or grayish-red color. The tissue of the diseased portions consists partly of hyperplastic granulations, partly of fibrillated connective tissue. If the former extend to the epithelial covering there appear partly hyperplastic, partly degenerative processes in the epithelial cells. The degeneration is characterized by the formation of vacuoles and by an infiltration of the parts with round cells. According to Stepanow, the vacuoles may contain bacilli.

The granulation tissue itself may show in many places no special peculiarities; it may, in fact, merely present the conditions that are found in other inflammatory infiltrations and proliferations of connective tissue. Other places, on the contrary, contain in smaller or larger numbers cells possessed of one vacuole, or completely degenerated and vacuolated, or reticulated in structure. In these gaps within the cells the bacilli can be detected (Fig. 374), some of which possess a gelatinous capsule. It is not to be doubted that the multiplication of the bacilli in the cells is the cause of the degeneration of the latter.

Along with the degenerated, vacuolated cells there occur cells of various shapes which have undergone hyaline degeneration (Fig. 375, *a*, *b*, *c*, *d*, *e*). These also contain bacilli with and without capsules, and also coccus-like forms. These cells may become changed into non-nucleated homogeneous scales by the loss of the nucleus (*d*). Finally, there are also cells inclosing hyaline spherules (Fig. 375, *f*, *g*), and these latter are also found lying free in the tissue (*h*). In places that are not yet affected with scar-degeneration the hyaline forms may be present in large numbers.

Fig. 374.

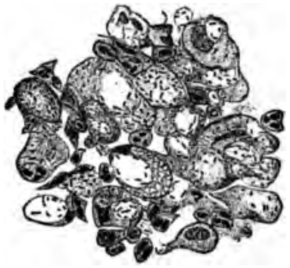

Fig. 375.

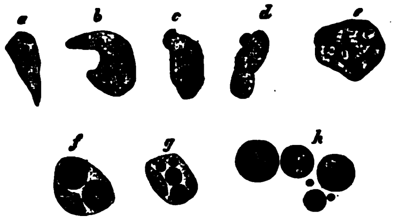

FIG. 374.—Section of rhinoscleromatous tissue, with numerous degenerated and vacuolated cells which inclose the bacilli. (Preparation of Stepanow, fixed in osmic acid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 400 diameters.)

FIG. 375.—Cells with hyaline degeneration and hyaline globules from rhinoscleromatous tissue of the vocal cord and of the nose. (Preparation of Stepanow.) *a*, *b*, *c*, *d*, Hyaline-degenerated cells with small bacilli; *e*, A hyaline cell with a capsulated bacillus; *f*, *g*, Cells with hyaline globules; *h*, Free hyaline globules. (*a*, *b*, *c*, *d*, stained with Löffler's solution; *e*, with hæmatoxylin; *f*, *g*, *h*, with fuchsin. Magnified 500 diameters.)

Bacillus xerosis is a fission-fungus, which has been described by Leber, Kuschbert, Reymond Colomiatti, Schleich, and Neisser. It occurs in xerosis conjunctivæ and appears in the form of short staves. The affection consists of a superficial disease—a sort of desiccation—of the epithelium of the conjunctiva bulbi. The conjunctiva loses its glistening appearance and becomes covered with small, white, fatty scales, which consist of horny and fatty-degenerated epithelial cells, free fat-droplets, and fission-fungi. The pathogenic significance of the bacilli has not yet been established, and is doubted by many authors.

§ 188. The **bacillus of blackleg** or **symptomatic anthrax** (*bactérie du charbon symptomatique*) is a staff 3 to 5 μ long and .5 to .6 μ thick, with rounded ends, and sometimes possessing independent motion (Fig. 376, *c*, *e*, *h*). According to the investigations of Bollinger, Feser, Arloing, Cornevin, Thomas, and others, it occurs constantly in blackleg.

§ 187. Under the name of the **bacilli of rhinoscleroma**, Frisch, Pellizari, Chiari, Cornil, Alvarez, Köbner, Paltauf, von Eiselsberg, Dittrich, and others have described short rods with rounded ends (Fig. 373) which constantly occur in the morbid formation called *rhinoscleroma* or *scleroma respiratorium* (Bornhaupt, Wolkowitsch), and consequently are regarded as the cause of the disease. Staining succeeds best with methylene violet; the sections being left in the mixture for from twenty-four to forty-eight hours. After staining, the sections are treated with iodine water, or are left for from one to three days in absolute alcohol.

The bacilli possess mostly a hyaline capsule. According to Paltauf, von Eiselsberg, Dittrich, Wolkowitsch, and others, they may be cultivated on blood-serum, gelatin, agar-agar, and potatoes; and under these conditions they form capsules (Fig. 373). When cultivated in bouillon, on the contrary, they show no capsules (Dittrich). Stab-cultures in gelatin resemble very much the nail-cultures of the pneumonia-bacilli of Friedländer, but are of a transparent grayish-white color, and not dead white. The bacilli stain more readily than the pneumonia-bacilli, and also stain by Gram's method. Stepanow observed, in inoculations into the eyes of guinea-pigs, active inflammations and proliferating granulations containing the bacilli and hyaline-degenerated cells.

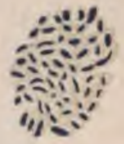

FIG. 373.—Bacillus of rhinoscleroma from an agar-agar culture three days old. (Preparation of Stepanow, stained with gentian violet, decolorized with oil of cloves and xylol, and mounted in Canada balsam. Magnified 750 diameters.)

Rhinoscleroma is observed principally in east Austria and in southwest Russia; isolated cases also occur in Silesia, Italy, Egypt, Belgium, Sweden, and Switzerland, and in South America. It is a chronic progressive disease of the tissues which lasts for many years, usually beginning in the nose (Wolkowitsch), more rarely in the throat, larynx, or palate, and extending thence to the neighboring parts—the external nose, lips, tear-passage, trachea, etc. The affection in the nose is characterized by a thickening of its walls which in some cases is diffuse, but in others is lumpy or nodular. The external skin assumes a reddish or brownish-red color, becomes stiff and cracked, and is covered with scales. In the throat and respiratory passages tough cartilaginous infiltrations are sometimes found, and at other times shrunken scar-tissue. The infiltrations may appear at times in the form of nodules or nodes, at other times in that of tumors and flat thickened areas; or, finally, they may be spread out more diffusely. By the transformation of the infiltration into shrunken scar-tissue extensive deformity of the affected organs may result. Deeply extending destruction of tissue is absent, but, on the other hand, superficial ulceration may take place. The infiltrated tissue on section appears yellowish and fatty, but not infrequently it shows a gray or grayish-red color. The tissue of the diseased portions consists partly of hyperplastic granulations, partly of fibrillated connective tissue. If the former extend to the epithelial covering there appear partly hyperplastic, partly degenerative processes in the epithelial cells. The degeneration is characterized by the formation of vacuoles and by an infiltration of the parts with round cells. According to Stepanow, the vacuoles may contain bacilli.

The granulation tissue itself may show in many places no special seat of inoculation, and is caused by an infiltration of the tissue with bloody œdematous fluid. The bacilli spread extraordinarily quickly, especially in the subcutaneous and intermuscular tissues (Fig. 376), and they also penetrate into the muscles. They cause severe lesions of the vessels, leading to hæmorrhage (Fig. 376, *f*) and to the exudation of a serous fluid; after a time an abundant emigration of leucocytes also takes place. Guinea-pigs usually die on the second or third day after the swelling has spread out over a portion of the body. The blood usually remains free from bacilli. Spores are not formed in the living body.

The **bacillus of swine-erysipelas** was described some years ago by Löffler, Lydtin, Schottelius, and Schuetz as a bacillus varying from 0.6 to 1.8 μ long. According to these investigations, it may be regarded beyond question as the *cause of swine-erysipelas* (*rouget du porc*).

Swine-erysipelas occurs especially in young hogs of the finer English breeds, whereas the commoner breeds are entirely or mostly insusceptible. The disease is characterized by fever, as well as by the appearance of red blotches on the neck, breast, and belly. The blotches subsequently become brown. Occasionally intestinal hæmorrhages also appear. More than half of the infected animals die, usually in a few hours or within four days. The autopsy reveals swelling of the intestinal mucous membrane, and here and there hæmorrhagic infiltration; swelling of the follicles and ulcers, especially in the region of the ileocæcal valve; swelling of the mesenteric lymph-glands; petechiæ in the serous membranes.

The bacilli are found in the blood, as well as in the lymph-glands, muscles, spleen, and kidneys, where they also lie in the vessels. Most of them are free, but some of them are inclosed in leucocytes. They can be stained by Gram's method.

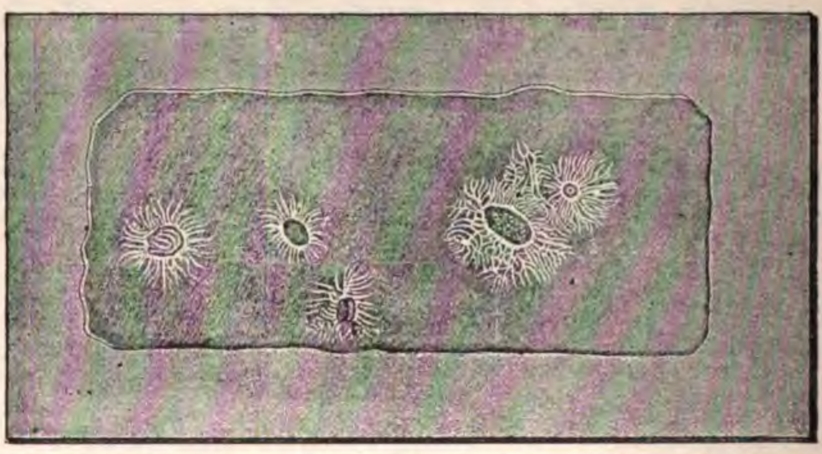

FIG. 377.—Plate-culture of the bacillus of swine-erysipelas. (After Schottelius.)

They may be cultivated at 18–40° C. in bouillon, as well as in infusion of meat containing peptone and gelatin, blood-serum and acid milk. The multiplication of the bacilli takes place constantly in the depth of the nutrient medium.

In gelatin poured out on plates they form peculiar radiating, branching figures (Fig. 377). In stab-cultures (Table I., Fig. 2) whitish rays grow out from all sides of the line of inoculation like the bristles in a test-tube brush. The bacilli may form pseudothreads in cultures. Glistening spherules which they sometimes inclose are regarded as spores. With the pure cultures swine-erysipelas can be reproduced in susceptible hogs. House-mice and doves die in from two to four days after inoculation, and their blood contains numerous bacilli.

On inoculation in rabbits an erysipelas-like inflammation results, which leads either to general infection, with fatal termination, or to recovery. Guinea-pigs and chickens enjoy immunity.

According to investigations of Pasteur and Thuillier, which were corroborated by Schottelius and Schuetz, the toxic power of the bacillus for swine decreases by continued reinoculation into rabbits. Susceptible hogs inoculated with vaccine attenuated in this way do not die from the inoculation, and become insusceptible to the fully virulent bacilli.

Chicken-cholera, also called *typhoid of fowls*, is an epidemic disease which occurs in chickens. The **bacillus of chicken-cholera** is a small bacillus 1 to 1.2 μ long, often somewhat constricted in the middle. It was first studied by Perroncito, and then by Toussaint, Pasteur, Rivolta, Marchiafava, Celli, and Kitt. The disease is characterized clinically by great debility and stupor, occasionally also by diarrhœal intestinal discharges; anatomically by swelling of the spleen and liver, by hæmorrhages and inflammations of the intestines, frequently also by pleuritis and pericarditis.

The bacilli are found in the blood, and consequently also in the capillaries of the various tissues. They may be cultivated on nutrient gelatin, on blood-serum, and in neutralized bouillon, as well as on potatoes, and they form whitish colonies. By inoculating or feeding chickens with the bacilli typical chicken-cholera can be produced. Pigeons, sparrows, pheasants, rabbits, and mice are susceptible to the bacilli. In sheep, horses, and guinea-pigs a local abscess at the seat of inoculation can be obtained.

According to Löffler* and Schuetz,† the swine-plague that occurs in Germany, and that formerly was often confounded with *swine-erysipelas*, is caused by a bacillus that has a strong resemblance to the bacillus of chicken-cholera.

The *American epidemic swine-diseases* are distinguished as two different kinds —namely, *hog-cholera* and *swine-plague*. According to Salmon, Billings, and Smith,‡ they are caused by different organisms. Selander§ also believes that the cause of the epidemic disease which is called *swine-pest*, and which has caused great destruction of hogs in Sweden and Denmark, is to be attributed to a bacillus.

Many other bacilli have, furthermore, been described as the causes of diseases that occur in animals. For example, according to Höflich ‖ and Enderlen,¶ the *pyelonephritis of cattle*, that is often observed, is caused by a *bacillus*. Also, according to Nocard,[*] the *farcy of cattle*, that often appeared formerly in France, and, according to Oreste and Armanni,[†] the epidemic disease of Italian buffaloes known as *barbone dei bufali*, are caused by a bacillus.

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* "Untersuch. über Schweinerothlauf," *Arbeiten a. d. K. Gesundheitsamte*, i., 1886.

† "Ueber die Schweineseuche," *Arb. a. d. K. Gesundheitsamte*, i., 1886.

‡ Cf. *Jahresbericht von Baumgarten*, 1886–1893, and *Centralblatt f. Bakteriologie*, 1887–1894.

§ "Die Bakterien der Schweinepest," *Centralblatt f. Bakt.*, iii., 1888.

‖ "Die *Pyelonephritis bacillosa* des Rindes," *Monatschr. f. prakt. Thierheilk.*, ii., ref. *Centralblatt f. Bakt.*, x.

¶ "Primäre infectiöse Pyelonephritis beim Rinde," *D. Zeitsch. f. Thiermed.*, xvii., 1891, ref. *Centralbl. f. Bakt.*, x.

The *Bacillus diphtheriæ columbarum* is a small, slender bacillus which Löffler[‡] isolated from the exudate of a pigeon dead of diphtheria. It is probably[§] the cause of pigeon-diphtheria, a disease resembling human diphtheria. Löffler was able to reproduce the disease in pigeons, but not in chickens, by inoculating pure cultures into the mucous membrane of the mouth. Mice died about five days after inoculation, and the bacilli were found in the blood-vessels of all the organs.

According to Löffler (*l. c.*), a *bacillus* is also found in the *diphtheria of calves;* but he did not succeed in cultivating it pure or in proving its pathogenic significance.

Diphtheria of fowls and *diphtheria of calves* are etiologically different from the diphtheria of human beings.[‖]

According to Koch,[¶] in decomposing fluids left uncovered in the early stages of putrefaction there often appear bacilli which closely resemble the bacilli of swine-erysipelas, both in appearance and in their behavior in cultures, and, when inoculated into house-mice, they multiply enormously in the blood and lead to swelling of the spleen. Mice die in from forty to sixty hours, in a crouched-up position. The bacillus is called the *bacillus of mouse-septicæmia* (*Bacillus murisepticus*). It may be easily stained with alkaline methylene blue, as well as by Gram's method. In the blood the bacilli are partly free, partly inclosed in leucocytes. The leucocytes are destroyed on account of the accumulation of bacilli in the interior of their bodies (Flügge). Field-mice and guinea-pigs enjoy immunity from the bacilli; doves and sparrows are susceptible.

§ 189. The fission-fungi that have been mentioned heretofore form staves, and according to the present method of classification belong under the bacilli. But there occurs in human beings, cattle, swine, and horses, still another fungus whose botanical position is not yet definitely determined. It may, however, best be classed with the polymorphic bacteria and placed in the list of bacilli. This is the **ray-fungus** or **actinomyces,** the cause of **actinomycosis**, a disease characterized by a progressively extending inflammation in which granulation tissue and connective tissue, as well as pus, are formed. It may be transferred by inoculation to rabbits and cattle.

Areas which the fungus forms in the tissues were long ago observed by Langenbeck and Lebert, but their significance was not rightly interpreted. The observations of Hahn, supplemented by the investigations of Bollinger and Harz, first led to a correct interpretation of the ray-fungus occurring in domestic animals. Israel found soon afterward a similar fungus in man, and Ponfick soon after gave his opinion in favor of the identity of actinomyces of cattle with the fungus discovered in human beings by Israel.

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[*] "Note sur la maladie des bœufs de la Guadeloupe connue sous le nom de Farcin," *Ann. de l'Inst. Pasteur*, ii., 1888.

[†] "Studii e ricerche intorno al barbone dei bufali," ref. *Centralbl. f. Bakt.*, ii., 1887.

[‡] *Mittheil. a. d. K. Gesundheitsamte*, ii.

[§] Babes and Puscarin, "Untersuch. über die Diphtherie der Tauben," *Zeitschr. f. Hyg.*, viii., 1890.

[‖] Esser, "Ist die Diphtherie des Menschen auf Kälber übertragbar?" *Fortschr. d. Med.*, vi., p. 324; Löffler, *Mittheil. a. d. K. Gesundheitsamte*, 1884; Pütz, *Fortschritte d. Med.*, v., p. 187.

[¶] "Untersuch. über die Aetiologie der Wundinfectionskrankheiten," Leipzig, 1878.

According to the investigations of Boström, the fungus that causes the disease is a higher fission-fungus that belongs to the species *Cladothrix*, and is distinguished from the bacilli in cultures on beef's blood-serum and agar-agar by the fact that it forms *branching threads*. The threads of the cultures are partly straight, partly wavy, sometimes also twisted like a screw. They break up by transverse division into short rods and coccus-like forms that grow out again into threads under suitable conditions.

Within the human and animal organisms the fungus appears in areas which may be in the form of little granules scarcely recognizable with the naked eye, or in that of spherules as large as two millimetres in diameter. The foci may be colorless and translucent, or white and opaque, sometimes yellow, sometimes brown, sometimes green, sometimes yellowish green in color. Of the smaller ones, quite a number consist only of a mat of fine threads, some of them branching, others straight or wavy or coiled-up.

Most of the granules contain, moreover, peculiar club-shaped forms (Fig. 378) that constitute the termination of the threads; and if these club-shaped forms are present in large numbers, as is usually the case in the larger foci, they have a radiated arrangement (Fig. 379, *a*) and lend a ray-like appearance to the fungus colony. Occasionally there develop hand- and fan-like forms on the ends of the threads (Israel). According to Boström, all these peculiar forms result from a swelling of the membrane of the fungus threads, and are to be regarded as retrogressive forms that appear upon the exhaustion of the nutrient material.

Fig. 378.

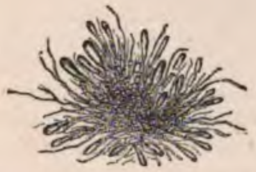

FIG. 378.—*Actinomyces hominis.* (Teased preparation. Magnified 800 diameters.)

Fig. 379.

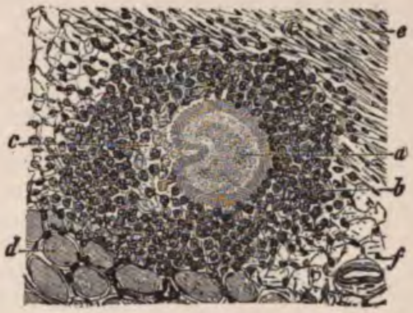

FIG. 379.—Section from a tongue affected with actinomycosis. *a*, Actinomyces kernel or gland; *b*, Cellular nodule; *c*, Pus-corpuscles; *d*, Cross-section of muscles; *e*, Longitudinal section; *f*, Cross-section of bands of connective tissue with blood-vessels. (Preparation hardened in alcohol, stained with alum carmine, and mounted in Canada balsam. Magnified 200 diameters.)

The actinomyces is usually taken up with the food or with the respired air, and finds its first development often in the cavity of the mouth. Since the threads and nodules of the actinomyces in many respects correspond exactly with the form of fungus called Leptothrix, and, moreover, since the club-like swellings also occur on the ends of the threads of the latter (Israel), it is difficult to determine the presence of the actinomyces in the cavity of the mouth, in which situation, moreover, it seems not to form the characteristic nodules. It has been impossible up to the present time to detect the organism outside the human body. But it must be remarked that often little bits of some higher plants—the beard of grain, a splinter of wood—have been found in the pus from an actinomyces focus, and that swallowing parts of plants—a spike of grain (Bertha)—or the contamination of wounds with vegetable material, preceded actinomycosis in some cases; so that it is very probable that the fungus occurs upon higher plants and upon wood.

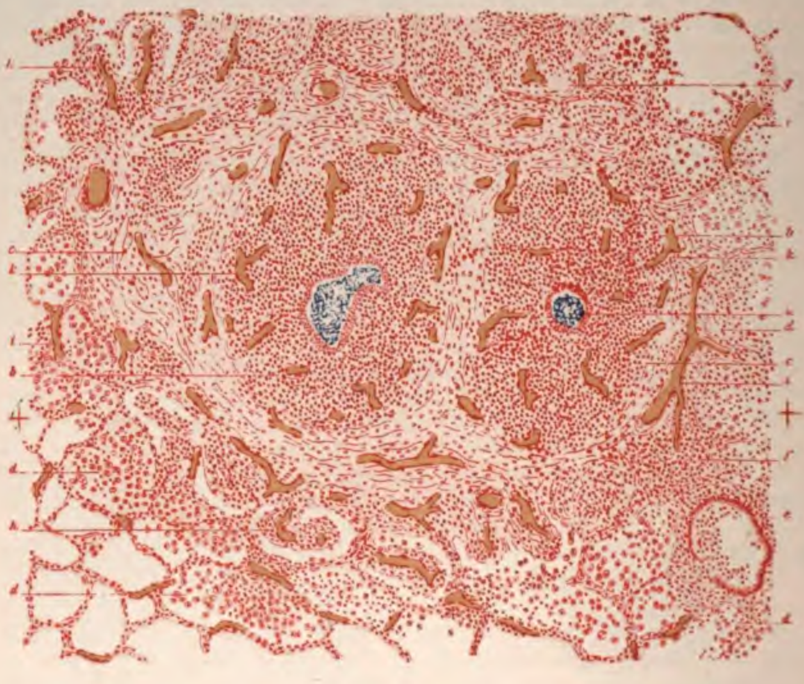

FIG. 380.—Actinomycosis of the lung. *a*, Fungus-kernel or gland; *b*, Small-cell nodule; *c*, Fibrous tissue; *d*, Alveoli filled with large and small cells; *e*, Bronchiolus with cellular-infiltrated wall; *f*, Small-cell focus in the neighborhood of the bronchus, *e*; *g*, Alveoli filled with vascularized connective tissue; *h*, Connective-tissue hyperplasia in alveoli; *i*, Blood-vessels of the lung-tissue; *k*, Blood-vessels of the inflamed area. (Preparation hardened in Müller's fluid, stained with carmine, and mounted in Canada balsam. Magnified 45 diameters. The actinomyces threads are put into the drawing from a preparation stained with gentian violet and magnified more strongly.)

If the ray-fungus succeeds in settling in a tissue it calls forth an inflammation in its surroundings. While the germ that has penetrated the tissue develops a mycelium and a fungus-kernel (Fig. 379, *a*, and Fig. 380, *a*), a nodular inflammatory focus forms in its surroundings, and this focus consists at first of small, round cells (Fig. 379, *b*, *c*, and Fig. 380, *b*), but later may also contain epithelioid cells and giant cells.

The fungus-kernels may multiply in the interior of a nodule and give rise to an enlargement of the latter, and it very often happens that cellular nodules the size of a pea and larger contain a large number of fungus foci, which are usually situated around the periphery. At the same time new fungus foci, and consequently new cellular foci, may appear in the neighborhood. The further spread of the infection takes place by means of small rods and threads, which probably break off from the larger masses and are observed partly free in the tissue, partly inclosed in cells.

Larger nodules often undergo, in time, in the middle a purulent melting down, and so lead to the formation of small abscesses, which may join together to form large pus-cavities or sinuses. In the neighborhood of the cellular foci (Fig. 380) a lively hyperplasia of the tissue quickly develops, and this leads to the formation of vessels (*k*) and of young granulation tissue, which subsequently becomes connective tissue (*c*, *g*, *h*). If the connective-tissue hyperplasia attains very considerable proportions it leads to induration (Fig. 380), often also to enlargement of the tissue. The hyperplasia may finally penetrate into the small-cell foci and supplant these, and the fungi are probably destroyed in this way.

If the hyperplasia gets the upper hand a nodular new formation of tissue ensues in the course of weeks or months, and in cattle it can reach the size of a man's fist, and may even considerably exceed this size. The tumor consists partly of dense connective tissue, partly of granulation tissue, partly of a tissue in a transitional stage between these, and always contains small cellular foci, or even cavities formed by disintegration, with fungus-kernels, of the shape already described, lying in the purulent contents. Where the fungus develops in the interior of the jaw-bone an active new bone-formation takes place simultaneously at the periphery.

If the destruction of tissue and pus-production predominate over the hyperplasia there result more or less extensive sinuous cavities and branching fistulous tracts anastomosing with one another. The walls consist of granulations and hyperplastic connective tissue, and here and there contain fungus foci. The clumps of fungi may become partially calcified.

In cattle the process is situated mainly in the lower jaw, then also in the upper jaw, in the tongue, in the throat-cavity, in the trachea, in the œsophagus, in the stomach, in the intestinal wall, in the skin, in the lung, and in the subcutaneous and intermuscular connective tissues. It leads here to the formation of more or less extensive nodular tumors of the character described, and was formerly given various names, such as osteosarcoma, bone-cancer, bone-tuberculosis, abscess of the jaw, wooden tongue, tuberculosis of the tongue, lymphoma, fibroma, worm-nodules, etc. In man the infection, as far as known, arises from the mouth or throat, or from the lung, or from the intestine, or from some external spot which has received an injury. In the first-named locality the invasion of the actinomyces takes its start from carious teeth (cavities or fistulæ), or from any injury to the soft parts of the jaw or of the cheek. Thence the process encroaches upon the neighborhood, and may finally extend to the face and the hairy portions of the head, as well as upon the throat, the nape of the neck, the back, and the breast.

Where the process appears for the first time, tumefactions take place that subsequently partially soften and give rise to fluctuation. Where the latter is the case, pus is formed that is sometimes thin fluid and sometimes more stringy, and contains the characteristic granules. If these abscesses break externally, fistulous tracts are formed, which either close again or continue to give off pus.

Accompanying the foci of suppuration, which are sometimes small, sometimes very extensive, there is formed constantly also more or less granulation tissue, which at times may be very abundant. In consequence of fatty degeneration and disintegration of its elements the granulation tissue often becomes partially whitish or yellowish or reddish white in color, and permeates the morbid tissue in an irregular manner. In other portions it returns to a development of connective tissue, especially in places where the process does not spread any further.

By this development of connective tissue a local healing of the process may take place, leaving behind a cicatricial induration. But usually in other places the process makes further progress, and under certain circumstances may lead to very extensive destruction. If it should encroach upon the bones of the spinal column or of the breast-wall these become roughened through superficial caries. In rare cases the jaw-bone may be attacked from the inside, as from an alveolus, and so undergo destruction. The process may spread inward from the base of the skull into the interior of the skull, and lead to actinomycotic meningitis and encephalitis.

According to Israel, in primary infection of the respiratory apparatus the process may run a long course as a mere catarrhal inflammation of the bronchi. More frequently the lung-tissue is affected from the start, and there may be bronchopneumonic inflammatory foci in which nodular foci (Fig. 380, *b*) form, assuming at an early stage a yellowish-white color in the centre. Here also cavities may be formed by disintegration of the inflammatory foci, and the contents of these will be found to consist of fluid, pus-corpuscles, fatty detritus, fatty globular granules, disintegrated red corpuscles, and masses of actinomyces. The tissue lying between the mycotic foci becomes to a greater or less extent affected with inflammatory thickening and induration, and may change by connective-tissue hyperplasia to a callous slate-gray or gray-and-white-colored mass which is devoid of air and later contracts. In this way the larger part of the lung may become changed into a mass of connective tissue.

The process sooner or later spreads from the lung to the visceral pleura, and thence to the costal pleura or over to the pericardium. In consequence of this, inflammatory exudates, as well as proliferative processes, take place at the locations mentioned, and lead to adhesions between opposite surfaces of the pleura and of the pericardium. The cellular infiltration, as well as the pus-formation and the fatty degeneration and disintegration of the granulation tissue, may extend between the ribs to the outside from the costal pleura, and spread in the contiguous soft parts, in the connective tissue and muscles, and finally break through, at different points externally. From the inside of the lung occasionally rupture takes place into the mediastinum and pericardium, and finally into the heart. Under certain circumstances rupture takes place through the diaphragm into the abdominal cavity, or the process spreads from behind the mediastinum into the retroperitoneal connective tissue.

The secondary areas of destruction situated outside the lung often assume perfectly colossal proportions, whereas in the lung the process may spread only to a limited extent and then cicatrize. At one time the purulent softening predominates, at another the formation of granulations and induration.

Actinomycosis originating in the intestinal tract begins with the formation of plaque-shaped, whitish patches of the fungus (Chiari), or of nodular mucous and submucous foci (Zemann) containing the fungus elements and leading to ulceration by undergoing necrosis. The process spreads from the intestine to the peritoneum and the retroperitoneal connective tissue, as well as to the organs adjacent to the original seat of disease—e.g., the liver. It finally breaks through the wall of the abdomen to the outside. Where the actinomyces patches develop, the inflammatory foci of hyperplasia are formed. If fæcal masses get into the tissues by a rupture of the intestine, fæcal abscesses are formed.

Metastases may occur in the course of the local disease, and this may take place by direct rupture of the fungus-growth into the blood-vessel, although this is rather unusual. From the intestines usually liver metastases result; from the lung there result skin, muscle, bone, brain, intestinal, and kidney metastases. The metastatic nodules behave like the primary foci. In rare cases primary foci of actinomyces occur in the internal organs—e.g., in the brain (Bollinger)—without our being able to discover any portal of entrance.

Johne, Ponfick, Boström, Wolff, and Israel have attempted inoculation experiments upon animals, and several of them (Johne, Ponfick, Wolff, and Israel) have obtained positive results, according to their statements. Wolff and Israel obtained in almost all cases a characteristic morbid condition, with inflammatory foci containing the fungus-masses, by the inoculation of rabbits and guinea-pigs. They also succeeded in cultivating upon agar-agar the fungus which they had taken from the tumors containing the masses of growth.

Eppinger[*] recently found a fission-fungus in the pus of an old brain-abscess which led to death by meningitis. The fungus is to be classed with the pleomorphic bacteria. Eppinger called it **Cladothrix asteroides,** and determined its characteristics by cultivation and inoculation upon animals. The disease caused by the fungus may be called **pseudotuberculosis cladothrichica,** since there existed, in the lungs and bronchial glands of the individual, changes similar to those which are observed in tuberculosis, and also since a disease suggestive of tuberculosis developed in guinea-pigs and rabbits on inoculation.

According to Dunker[†] and Hertwig,[‡] there occurs in hogs a ray-fungus which is always situated in the muscles, especially the intercostal muscles and those of the diaphragm and abdomen. It causes a degeneration of the muscle-fibres of the surrounding neighborhood, and hyperplasia of the connective tissue. The masses of fungi are also arranged radially, forming club shapes. They readily undergo calcification and then form white points in the flesh.

According to the investigations of Kanthack,[§] Boyce,[||] and Vincent,[¶] it is very probable that the affection known as **Madura disease,** or **Madura foot,** or **mycetoma,** observed in India, represents a disease caused by a polymorphic fission-fungus nearly related to actinomyces and called by Vincent *Streptothrix Maduræ.* The disease consists of a gradual swelling of one of the extremities, caused by nodular deposits which turn into abscesses and fistulous tracts, on pressure emptying peculiar brown or black fish-roe- or truffle-like granules. The gran-

[*] "Ueber eine neue pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberculosis," *Beiträge zur path. Anat. von Ziegler*, ix., 1891.

[†] *Zeitschrift f. Mikroskopie und Fleischschau*, iii., 1884.

[‡] *Archiv f. wissensch. u. prak. Thierheilk.*, xii., 1886.

[§] "Madura Disease and Actinomyces," *Journal of Pathology*, i., 1892.

[||] "Upon the Existence of more than one Fungus in Madura Disease," *Philos. Trans.*, vol. clxxxv., 1892; and *Hyg. Rundschau*, 1894.

[¶] "Étude sur la parasite du pied de Madura," *Annal. de l'Inst. Pasteur*, 1894.

ules contain the fungus. Kanthack even regards the fungus as identical with actinomyces; but the investigations of Vincent and Boyce do not agree with this assumption. According to Boyce, the *Streptothrix Maduræ* forms two varieties: a white one with white dichotomously dividing threads, and a black one with branching pigmented threads. Formerly it was assumed that the Madura disease was caused by a thread-fungus, the *Chionyphe Carteri*,[*] but there are no convincing investigations to support this assumption.

3. *The Spirilla and the Morbid Processes Caused by Them.*

(*a*) *Non-pathogenic Saprophytic Spirilla.*

§ 190. The **spirilla** or **spirobacteria** are divided into two genera, one of them called Spirillum, the other Spirochaete.

The genus **Spirillum** is characterized by the formation of stiff, short, shallow spirals, which sometimes have flagella and possess lively motion. Wavy staves are also called *Vibriones* by many authors.

Spirillum sive *Vibrio rugula* (Fig. 381, *b*) forms staves from 6 to 16 μ long and from 0.5 to 2.5 μ thick, simply bent or having a shallow turn, which move themselves by means of a flagellum. The spirillum occurs in water from swamps, in fæces, and in slime from the teeth.

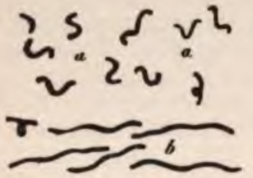

FIG. 381.—*Spirillum* sive *Vibrio rugula*, *b*, and *Spirillum undula*, *a*, obtained from a cold infusion of finely chopped earthworms. (Drawn from a dried preparation treated with gentian violet. Magnified 600 diameters.)

Spirillum sive *Vibrio serpens* forms thin threads from 11 to 28 μ long, with three or four wavy bands. It occurs in stagnant fluids.

Spirillum tenue has threads from 3 to 15 μ long, very thin, with from two to five spiral turns.

Spirillum undula (Fig. 381, *a*) is a thread 1 or 1.5 μ thick and from 8 to 12 μ long, bearing on its end a flagellum and having from one and a half to three turns. It occurs in various putrefying fluids and executes rapid twisting and darting motions.

Spirillum volutans possesses threads 1.5 or 2 μ thick and from 25 to 30 μ long, with from two and a half to three and a half turns, bearing a flagellum at both ends.

The species **Spirochaete** (Fig. 384) is characterized by flexible, long, sharply turned spirals.

Spirochaete plicatilis forms threads from 100 to 225 μ long, very fine and closely turned. It is very abundant in water from marshes and gutters, and executes very rapid movements.

Spirochaete buccalis sive *denticola* is from 10 to 20 μ long, pointed at both ends, and is not infrequently observed in the secretion from the cavities of the mouth and nose (cf. Fig. 153). It seems to have no pathogenic significance.

The spirilla, as far as they are not pathogenic, are little known, and investigations particularly as to their life-history are wanting. They are present in large numbers in the contents of privy-vaults. According to Prazmowski, *Spirillum rugula* causes decomposition of cellulose and forms spores at the ends of the spirilla. According to Weibel, a vibrio which occurs in nasal slime has manifold forms of growth. Esmarch succeeded in cultivating a spirillum, called by him *Spirillum rubrum*, in the different ordinary media. In bouillon it forms spirals of from forty-three to fifty turns. Short spirilla execute lively motions, but long spirilla, on the contrary, sluggish motions, or they may be motionless. Colonies in solid media are at first pale, but assume afterward in portions not in contact with air a wine-red color. In spirilla of old cultures three or four dull, glistening spots occur that do not stain and are probably to be interpreted as spores. Cultures containing spirilla of this kind are more resistant to drying than others; but they are, on the contrary, very easily killed by heat.

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[*] Carter, "Mycetoma, or the Fungus Disease of India," London, 1874; Lewis and Cunningham, "The Fungus Disease of India," Calcutta, 1875; Hirsch, *Virchow's und Hirsch's Jahresbericht*, 1875 and 1876.

The long spirals may break up into short segments possessing only about three quarters of a turn, and these grow out in length and again divide.

(*b*) *The Pathogenic Spirilla.*

§ 191. **Spirillum choleræ Asiaticæ,** also called *comma-bacillus* (*bacille-virgule cholérigène*), was discovered by R. Koch in 1884 and recognized as the cause of Asiatic cholera (Fig. 382). It is constantly found in the dejecta of those suffering from Asiatic cholera, and forms a small, comma-like, curved staff from 0.8 to 2 μ long.

Cultures of the cholera-spirilla are obtained upon a great variety of slightly alkaline media. The temperatures favorable for their growth are between 25° and 37° C. Between 16° and 8° C. they are still capable of puny development (van Ermengem).

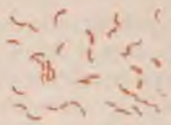

FIG. 382.—Cholera-spirilla from a pure culture. (Cover-glass preparation colored with fuchsin. Magnified 400 diameters.)

On gelatin plates they form round, flat, yellowish disks which liquefy the gelatin only slowly. With low magnifying powers they appear irregular in outline, and the surface granular or grooved and rough; it conveys the impression as if the surface were strewn with small particles of glass (Koch). By the liquefaction of the gelatin in the immediate neighborhood a funnel-shaped cavity is formed, and the colony sinks down finally to the bottom of the cavity.

Stab-cultures in gelatin form in two days a whitish cord corresponding to the line of inoculation (Table I., Fig. 3). The gelatin becomes liquefied immediately around the line of inoculation. The canal widens out upward into a funnel filled with liquefied gelatin below and with air above. The widening of the funnel of the canal of inoculation takes place slowly, so that its edge reaches the wall of the tube only after five or six days.

On potatoes at 30–35° C. the spirilla form light-brown cultures, on agar-agar grayish-yellow slimy cultures. They grow, moreover, also in bouillon, blood-serum, and milk.

They do not increase in pure water (Bolton), but in water that is contaminated with substances which furnish nutrient material.

The cholera-spirilla are aërobic, but they also are able to grow when oxygen is cut off. According to the investigations of Hueppe, cultivation in the presence of a paucity of oxygen increases the toxic power of the cultures; but, on the contrary, the resisting power against injurious agents—e.g., against acids and similar substances—is diminished; with free admission of oxygen the reverse takes place. Pfeiffer, however, found that young cultures cultivated in oxygen also contained poison. The spirilla present in fresh dejecta are easy to kill (Hueppe) and but little suited for infection, whereas the growth of the spirilla outside the body increases their resisting power against the stomach-juices, etc., and makes them more suitable for the infection of new individuals. They are readily destroyed by desiccation in free air (Guyon), by high temperatures, and by boiling for a short time. They are easily supplanted by saprophytic bacteria where the nutrient material and the temperature are not entirely suitable. In privy-soil they die out quickly, according to Koch. They are readily destroyed by acids, corrosive sublimate, and carbolic acid. According to the observations of Koch, they can be preserved in well-water thirty days, in sewage seven days, on moist linen three or four days. Nicati and Rietsch found them alive after eighty-one days in water taken from the harbor of Marseilles.

In cultures they form sometimes short rods more or less curved (Fig. 382) and often hanging together in twos, sometimes long spirals. Along with these forms there also occur straight staves, and sometimes the majority of the rods that are present show the curve only imperfectly or not at all. In fluid media to which oxygen has access they show lively motility, which is easily seen in a hanging drop. According to the investigations of Löffler, the motility is caused by a single flagellum on one end.

When the nutrient material is exhausted to a certain extent, involution-forms often appear, in which the rods are sometimes shrunken, sometimes swollen, thus causing them to present a variety of forms. Globular swelling, as well as uncolored places in stained preparations caused by degeneration, have often been erroneously regarded as phenomena of fructification. Formation of spores has not been proved. If hydrochloric or sulphuric acid is added to cultures of the cholera-bacilli in culture-media containing peptone, the cultures assume a rose or Burgundy-red color, due to the formation of a coloring-matter—*cholera red*. A suitable culture-medium for this reaction is a meat-infusion containing peptone, or a 1 per cent. solution (rendered alkaline) of peptone containing 1 per cent. of salt. According to Salkowski, this is a nitroso-indol reaction.

When they get into the intestinal tract of human beings the spirilla develop in the small as well as in the large intestines, so far as they are not destroyed by the action of the gastric juice and are not hindered in their development by other influences. Their growth is followed by an extensive transudation from the intestinal mucous membrane, so that the intestine is filled with a fluid resembling meal-soup or rice-water, in which flakes of desquamated and slimy epithelial cells float about.

The spirilla are always present in large numbers in the contents of the intestine, and are also found in the lumen of the intestinal glands, and they may penetrate from there between and under the epithelial cells.

In fresh cases the presence of the spirilla may be demonstrated usually by making a cover-glass preparation stained with methylene blue or with fuchsin. The fresh dejecta, as well as foul clothing, are suitable for the examination, since, according to Koch's observations, the spirilla can multiply for a while vigorously on moist linen and moist earth. In old cases the detection of the spirilla is more difficult, but nevertheless succeeds in all cases, according to a number of authors (Koch, van Ermengem, Nicati, Rietsch, A. Pfeiffer, Babes, Ceci, Schottelius, and others), and is attainable most surely by making plate-cultures. In order to facilitate the separation of the cholera-spirilla from the other intestinal bacteria, Schottelius recommends the mixing of the dejecta with double the amount of meat-infusion rendered slightly alkaline, and allowing the mixture to remain uncovered at a temperature of 30–40° C. for twelve hours. The spirilla, requiring oxygen as they do, develop especially on the surface, and may be easily transferred thence to plate-cultures. Koch recommends for this purpose a solution of peptone with salt.

Alkaline methylene blue is used for staining sections of the intestines.

The presence of cholera-spirilla in the intestines excites inflammation, which finds expression at the start in reddening, swelling, transudation, mucoid degeneration of the epithelium, and desquamation; subsequently also in hæmorrhages, formation of sloughs, and ulceration. It is characterized constantly by a more or less abundant cellular infiltration of the tissues. The solitary follicles and Peyer's plaques are swollen even in fresh cases. Death may take place in a few hours or in from one to three days. If the disease lasts longer the contents of the intestines become more consistent and the intestinal mucous membrane shows ulcerative changes.

According to present experience, the spirilla produce poisonous substances which cause local damage to the mucous membrane of the intestinal canal, phenomena of intoxication, and paralysis of the vessels. In the liver and kidneys there often result small foci of degeneration, and within these the cells of the glands are cloudy or fatty and affected with hyaline degeneration or necrosis. Moreover, the kidneys very often show cloudiness caused by toxic degeneration of the epithelium; also there is occasionally swelling of the cortex. Frequently there are also ecchymoses in the epicardium; in the later stages also patches of necrosis in the mucous membrane of the vagina. The presence of the spirilla for a long time in the intestines may be followed by the formation of ulcers. Eventually they are crowded out by the putrefactive bacteria present in the intestines, and die out. A new intoxication, not dependent upon the original spirilla, may result from absorption of the products of putrid decomposition.

According to Koch, Nicati, and Rietsch, the cholera-bacilli may be contained in the material vomited. Nicati, Rietsch, Tizzoni, and Cattani also found them in the ductus choledochus and in the gall-bladder. According to the statement of these authors, the spirilla do not usually get into the blood, and are also absent from the internal organs; nevertheless Tizzoni and Cattani were able to demonstrate their presence in the cerebrospinal fluid, which was increased in amount, and they also found them in the blood of an aborted fœtus, five months old, from a woman sick with cholera.

Koch detected the spirilla in a tank in India which furnished the inhabitants with their entire supply of water for drinking and other purposes, at a time when a part of the inhabitants were sick and dying of cholera. Since then they have been often detected during cholera epidemics in water-supplies.

According to the investigations of Nicati, Rietsch, van Ermengem, and Koch, symptoms resembling cholera can be produced in experimental animals by the introduction of cholera-spirilla into the intestinal canal. This succeeds when cultures are introduced directly into the duodenum or small intestines (Nicati and Rietsch); also (Koch) by rendering the gastric juice of the animals (guinea-pigs) alkaline with a 5 per cent. solution of soda, then quieting the bowels by injecting into the abdominal cavity 1 ccm. of tincture of opium to every 200 grammes of weight of the animal, and finally introducing one or several drops of a pure culture into the stomach.

Animals inoculated in this way die with severe symptoms of collapse. The small intestines are found to be filled with a watery, flocculent fluid containing numbers of spirilla; the intestinal mucous membrane is reddened and swollen.

Asiatic cholera is endemic in Lower Bengal, and never entirely disappears there. Thence it spreads at times over India and over a larger or smaller territory of the earth by transportation. Since the spirilla easily perish outside the body, the transportation must be effected mainly by persons suffering from cholera. Infection probably occurs exclusively from the intestinal canal by the introduction of infected beverages or food or some other substance into the mouth. But it is certain that the introduction of cholera-spirilla into the intestinal canal is not always followed by the disease.

Moreover, it not infrequently happens that the spirilla increase in the intestines, but only cause slight changes, so that the infected person suffers no severe trouble, and the diagnosis can be only made by the detection of the spirilla in the stool.

If the cholera-spirilla get into the drinking-water or water-supply in general, and succeed in multiplying, the cholera may develop with extraordinary rapidity in the locality. If, on the contrary, the infection follows by direct or indirect contagion from one person to another, the spread takes place more slowly, since it is limited to those who come in contact with the sick person or with the articles contaminated by the latter. The period of incubation lasts one or two days.

In the intestines of convalescents, according to investigations of Kolle, the spirilla may continue to live for a long time and to multiply, without giving rise to any symptoms that point to their presence. Kolle was able to detect them in a number of cases after from five to eighteen days, and in some cases even after from twenty to forty-eight days.

Once recovered from the disease, the affected individual enjoys immunity for a certain length of time.

The poison which the cholera-spirilla produce, and which mainly causes the symptoms of cholera infection, is unknown. Gamaleia believes that it is a nucleo-albumin, Scholl that it is a peptone (cholera toxopeptone). Pfeiffer is of the opinion that it is a component part of the cell-body. Emmerich and Tsuboi seek to prove that the morbid phenomena in cholera are due to a nitrite-poisoning. They call attention to the fact that nitrites in small doses cause retching, vomiting, discharge of thin-gruel fæces, fall of temperature, weakness of the heart, cyanosis, and cramps of the extremities and muscles of the neck—in other words, symptoms resembling an attack of cholera; and, moreover, that the cholera-spirilla are able to make nitrites out of the nitrates contained in nutrient substances.

The virulence of cholera-cultures differs greatly, according to the source and the age. With increasing age the virulence decreases. Guinea-pigs, although very susceptible to intraperitoneal infection with cholera, may be protected from infection by intraperitoneal inoculation with attenuated cultures; but no absolute immunity can be brought about in this way. Blood-serum of human beings that have recovered from an attack of cholera shows protective properties for guinea-pigs some weeks after the attack.

The production of the nitroso-indol reaction in cultures of the cholera-spirilla is due to the fact that the cholera-spirilla not only produce indol in peptone solution, but also nitrites. For this reason, nitrous acid is liberated by the addition of hydrochloric or of sulphuric acid, and makes a red color with the indol. With the Finkler spirillum, the spirillum of Metschnikoff, and the spirillum of Deneke, which also produce indol, the red color of the cultures only occurs when potassium nitrite is added along with sulphuric acid, or when nitrous acid is added.

The following spirilla resemble the cholera-spirilla:

1. *Spirillum of Finkler and Prior*, found by the authors named in the dejecta of persons suffering from cholera nostras, which had stood for some time in a vessel. The spirilla are very much like the cholera-spirilla, only somewhat longer and thicker. In plate-cultures they are distinguished from the latter in that the small colonies are not distinctly granular and have a sharp contour. Gelatin is rapidly, not slowly, liquefied; and consequently after twenty-four hours a sac-like tube (Fig. 383) filled with a cloudy fluid is formed in stab-cultures and rapidly spreads to the walls of the tube.

According to Flügge, even in forty-eight hours at room-temperature they form a grayish-yellow slimy coating, sharply marked off from the substance of the potato by its whitish border; whereas the cholera-spirilla do not grow at room-temperature at all, and at a higher temperature form a brown coating.

They, moreover, cause a foul-smelling decomposition and are rather resistant to drying. When introduced into the intestines of guinea-pigs by the method above described, they operate similarly to the cholera-spirilla, but less intensely.

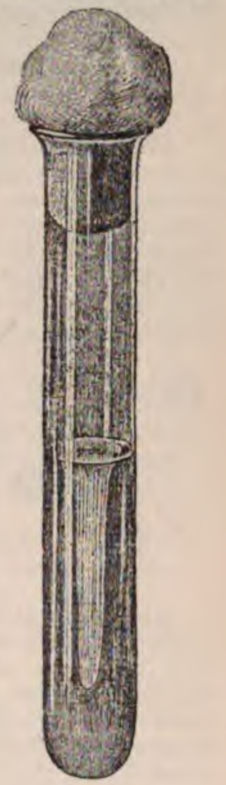

FIG. 383.—Stab-culture of the Finkler-Prior bacillus in gelatin.

It is very questionable whether the Finkler-Prior spirilla have pathological significance for cholera nostras, since the dejecta from which the investigators made their culture were not fresh, and other authors in similar cases have not found the spirilla.* Knisl† found them in the contents of the cœcum of a suicide.

2. *Spirillum tyrogenum*, found in cheese by Deneke‡ in Flügge's Institute, is also very much like the cholera-spirillum, but it is somewhat smaller and the long spiral threads are more narrowly wound. Cultures on gelatin plates form at first sharply contoured disks that appear dark with lower magnifying powers. They liquefy the gelatin much more quickly than do the Koch spirilla. In the line of puncture they behave similarly to the Finkler-Prior spirilla, but do not grow on potatoes.

3. *Spirillum sputigenum* is a spirillum whose shape is that of a curved staff,

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* Kartulis, "Zur Aetiologie der Cholera nostras," *Zeitschrift f. Hyg.*, vi., 1889.

† *Münchener ärztliches Intelligenzblatt*, 1885.

‡ *Deutsche med. Wochenschrift*, 1885.

somewhat longer and thinner than the cholera-spirillum. It occurs in saliva and cannot be cultivated on the media that are in use.

4. *Vibrio of Metschnikoff* * is a fission-fungus that Gamaleia was able to isolate in an epidemic of chickens in Odessa which was characterized by the appearance of diarrhœa and enteritis. On cultivation it shows very great resemblance to the Koch spirillum. The spirillum is most easily obtained pure by inoculating pigeons with the blood of diseased chickens. The pigeons die in from twelve to twenty hours and show the spirilla in the blood and in the intestinal tract.

§ 192. The **Spirochaete Obermeieri** (Fig. 384) is found constantly in the blood of patients suffering from **relapsing fever**, during the attack of fever, and their multiplication in the body is the cause of the disease.

It is from 16 to 40 μ long and possesses numerous turns. In a fresh drop of blood it exhibits lively motion. Carter and Koch succeeded in producing the disease by inoculating apes with the spirochaete. But nothing definite is known as to their development and their habitat outside the blood. It is also unknown where they or their spores are to be found in the afebrile stages of the disease. In apes an attack of fever occurs only after several days have elapsed since the subcutaneous injection of blood containing the spirochaete. According to the pathologico-anatomical results observed in man, it is to be noted that the spleen is enlarged and often contains numerous yellowish foci of degeneration, and often also anæmic infarctions.

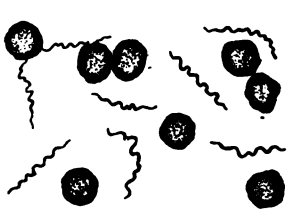

FIG. 384.—*Spirochaete Obermeieri* from the blood of a person suffering from relapsing fever. (From a dried preparation treated with methyl violet. Magnified 500 diameters.)

According to the investigations of Nikiforoff, the histological examination of the spleen reveals extensive necrosis of cells and cell-degeneration, as well as exudation of fibrin in the veins of the pulp and hyperplastic processes in the cells of this part of the spleen. Moreover, numerous large pulp-cells inclose decolorized red blood-corpuscles or fragments of these. Finally, numerous spirilla are found, especially in places which, while not entirely necrotic, nevertheless contain degenerated and necrotic cells, partly free, partly inclosed in leucocytes. Of the remaining cells some are well preserved, while others are just beginning to show signs of disintegration.

For staining this variety of spirilla in preparations dried on cover-glasses, alkaline methylene blue and fuchsin are most suitable.

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* Gamaleia, "*Vibrio Metschnikovi* et ses rapports avec le microbe du choléra asiatique," *Ann. de l'Institut Pasteur*, ii., 1888; iii., 1889; and Pfeiffer, "Ueber den *Vibrio Metschnikovi* und sein Verhältniss zur Cholera asiatica," *Zeitsch. f. Hyg.*, vii., 1889.

SECTION X.

Mould-fungi and Yeast-fungi, and the Pathological Tissue-changes Caused by Them.

§ 193. **Mould-fungi** and **yeast- or budding-fungi** belong to the non-chlorophyl-bearing thallophytes, as the fission-fungi do. They have no near connection, particularly in the phylogenetic sense, with the fission-fungi. On the other hand, they stand in very close relationship with one another (Brefeld, Nägeli, de Bary).

Mould-fungi and yeast-fungi, like the fission-fungi, are compelled to derive their nutrition from organic substances containing carbon. The majority find it in dead organic substances, and therefore belong to the *saprophytes*. Some of them are capable of deriving nutrition from living tissues, and are to be classed, occasionally at any rate, as *parasites*. In human beings both kinds occur.

Outside of the organism the mould-fungi are universally known as the producers of the different mouldy coverings that so often develop on organic substances. They belong to various groups of fungi.

The yeast-fungi are the producers of alcoholic fermentation and they form the scum on the top of alcoholic beverages.

The systematic classification of the thallophytes has experienced many alterations in recent years. Formerly they were divided into algæ, lichens, and fungi, the distinction being based mainly upon peculiarities of habit and upon differences of outward appearance and mode of life. Subsequently not only were the morphological relations of growth explained, but the sexual organs were found; and in many cases it was found possible to follow the entire history of development. After this the tendency was to classify some groups of fungi with the algæ—namely, the non-chlorophyl-bearing forms that are morphologically similar to the chlorophyl-bearing thallophytes. According to de Bary, however, this morphological analogy is of a secondary nature. The fungi form for themselves a morphological cycle that has no near relationship to the bacteria.

Brefeld * expressed the opinion that different yeast-fungi are only conidia forms of various other fungi which can multiply by endless budding in and upon nutrient solutions. He bases his opinion upon the fact that different fungi —for example,the fungi causing blight—can increase for a long time by yeast-like budding without being transformed into the other form, and that these ferments are morphologically like the common yeast. Whether they also physiologically resemble it he does not say, and consequently the possibility that the budding fungi form an independent type is not excluded.

According to de Bary and Rees, the budding fungi are to be regarded as a special type, and are to be put in near relationship to the ascomycetes. Nägeli also recognized the independence of the budding fungi and sought their nearest relations in the mould-fungi. He bases his opinion upon the fact that the mucor varieties also form ferments.

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* "Botanische Untersuchungen über Hefenpilze," 1883.

§ 194. **Mould-fungi** are found in man partly in the form of simple or branching, unjointed or jointed threads of varying thickness; partly in that of oblong or even globular cells. The threads are called **hyphæ** (Figs. 385 and 386), and the mass which they form **mycelium**; the spherical or long oval or short cylindrical cells, which often hang together like a rosary, are called *spores* or, better, **conidia spores** (Figs. 385 and 386). Fructification on special fruit-bearers inside the body is only rarely observed.

Fig. 385.

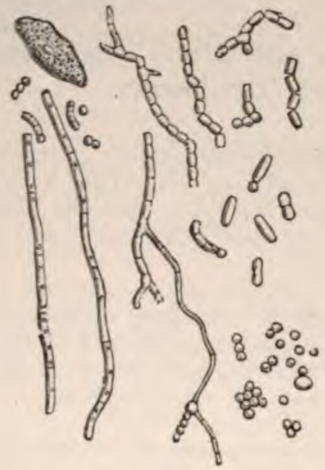

Fig. 386.

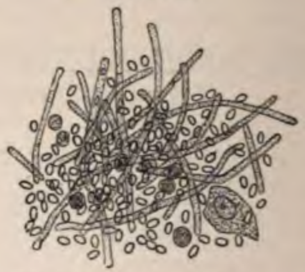

Fig. 385.—Hyphæ, conidia, and epithelial cells from a fresh specimen of favus. (After Neumann.)

Fig. 386.—From a deposit of aphthæ on the tongue of a man who died of typhoid fever. (Magnified 300 diameters.)

The mould-fungi are partly saprophytes and partly parasites, and are found, with but few exceptions, only in localities exposed to the outside, as on the skin (Fig. 385), in the intestinal canal (Fig. 388), in the respiratory apparatus, in the external auditory passage, in the vagina, etc. Only exceptionally, and under special conditions, do they penetrate to the internal organs, as, for example, the brain. It is clear that the living tissues of the human organism do not afford a suitable nutrient medium for the mould-fungi, and the living activity of the tissue-cells for the most part does not allow development and multiplication of these. The need for oxygen does not allow the mould-fungi to develop in many tissues, and the body-temperature is, moreover, too high for many of these fungi. The chemical composition of the tissues, also, does not form a favorable mixture of nutrient material for the mould-fungi.

In general the **yeast-fungi** find a deficiency of fermentable saccharine fluids in the organism. Only in the upper part of the intestinal canal—e.g., in the stomach, and also, in diabetes, in the bladder—do saccharine fluids remain long, and in these situations development of budding fungi and alcoholic fermentation can take place. In the stomach budding fungi are almost always to be found.

In solutions containing sugar the budding fungi produce oval cells (Fig. 387). Reproduction takes place by means of budding and constriction (Fig. 387)—i.e., on any portion of the mother-cell there arises an excrescence, which is constricted off after it has attained the size of the mother-cell. Under certain conditions the cells can grow out into threads, but no subsequent segmentation takes place in these threads; jointed threads result from budding (Cienkowsky, Grawitz). Diluted nutrient fluid favors the formation of threads.

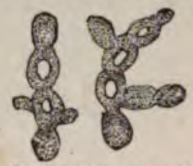

FIG. 387.—*Saccharomyces ellipsoideus.* (Magnified 400 diameters.)

Mould-fungi that grow as saprophytes occur most frequently in the *alimentary canal* in man, and here again most frequently in the *mouth, throat,* and *œsophagus,* and develop here particularly in the stomach when ingesta remain a long time, or in the mouth-cavity when desquamated cells accumulate and interfere with the function of the organ in question. They are recognizable by the formation of threads and conidia.

In the *external ear-passage* the mould-fungi are especially apt to grow in abnormal masses that fill up the passage and that consist, in some instances, of the secretion of the sebaceous glands of the ear, in others of inflammatory exudates and desquamated epithelium, and in still others of substances introduced from without.

Inside the *lung* the mould-fungi occasionally grow in the necrotic walls of cavities formed by disintegration, such as occur especially in tuberculosis, and they also grow in necrotic and gangrenous hæmorrhagic infarctions. In the region of the air-passages they are oftenest observed in bronchi-ectases.

In the intestinal canal, as well as in the ear and in the lung, the mould-fungi usually form white deposits on or in the tissues. On the appearance of fructification (upon special fruit-bearers) they may, however, in places present a brown, gray, or black appearance. In the intestinal canal beverages and food may give them various colors.

All of these fungi have their habitat first in dead material, but they may penetrate thence more or less widely into living tissue; and cases have been observed in which they had even penetrated into the circulation and were carried by the blood-current to distant organs. Thus the fungus-growth called **aphthæ,** which appears mostly in the cavity of the mouth, the throat, the œsophagus, more seldom in the stomach, in the small intestines, and in the vagina, and on the nipple of the breast of nursing women, cannot be regarded as a pure parasite, but, on the contrary, as a *parasitic growth* which penetrates into living epithelium (Fig. 388, *c*) and even into the connective tissue lying below. It is true that aphthæ for the most part occur only in depleted sick persons who are no longer able to cleanse the mouth, throat, and œsophagus, and whose condition of nutrition has suffered, as well as in sucklings. Consequently special local primary conditions are necessary for its development, and the primary colonization of the fungus probably occurs in substances that have died. Still an active penetration into living tissue takes place (*c, d*), and from these portals of invasion even metastases may develop in internal organs. Thus Zenker observed fungus threads and conidia in an abscess of the brain, and Paltauf reported a case in which a mould-fungus was conveyed from an intestinal ulcer to the brain and lung. Schmorl described aphthæ metastases from the kidneys.

The mould-fungi which grow in the lung do not always confine themselves to tissue that has died out or to the interior of the bronchus; they can also get into living, respiratory parenchyma (although rarely, it is true), and when they invade this locality they form small white nodular masses (Boyce) in the neighborhood of which the lung-tissue is infiltrated.

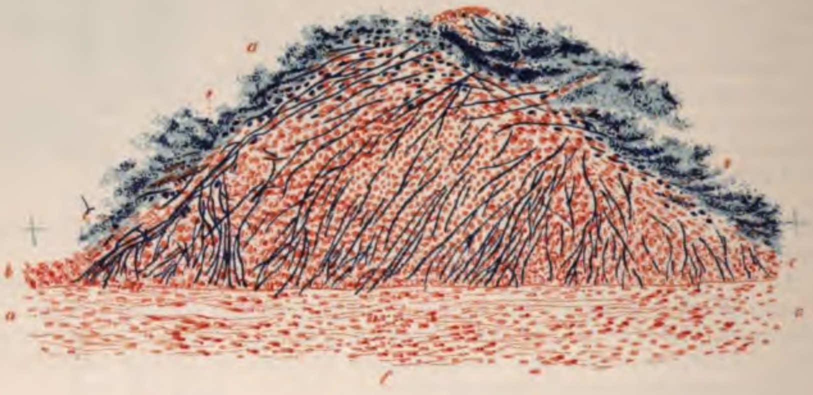

FIG. 388.—Section through an aphthæ-covered œsophagus of a small child. *a*, Normal epithelium; *b*, Connective tissue; *c*, Swollen and desquamated epithelium permeated with the growth of fungus threads; *d*, Epithelium infiltrated with cells; *e*, Masses of cocci and bacilli; *f*, Cellular focus in the connective tissue. (Preparation hardened in alcohol, stained with carmine and also according to Gram's method, and mounted in Canada balsam. Magnified 100 diameters.)

Local colonizations of mould-fungi which penetrate into living tissue exercise a more or less considerable irritation in the neighborhood, and cause degeneration (Fig. 388, *c*) and inflammation of the tissue. This can be observed in mycosis of the lung, as well as in intestinal mycosis (*c*, *d*, *f*) and mycosis of the ear. When they have penetrated into the lung they form growths which are similar to the actinomyces nodules and are surrounded by an accumulation of cells (Boyce). Their action, however, is always limited, and, furthermore, they produce no substances which are injurious to the whole organism or cause symptoms of poisoning. The finding, as has been frequently reported, of mould-fungi in abscesses of the internal organs is probably to be interpreted in this way: that, along with fission-fungi which cause suppuration, thread-fungi get into the tissues and thence also into the circulation. A general spreading of mould-fungi does not occur even in these cases, because the further development remains confined to the location of the metastasis.

As recent investigations have shown, the forms of mould-fungi which are saprophytic, or at least pathogenic only under certain circumstances and to a limited extent, belong to the **Mucor, Aspergillus,** and **Eurotium** families. Several species have been obtained from the ear, and have been designated as *Aspergillus fumigatus* (Fresen), *Aspergillus flavus* sive *flavescens* (Brefeld, Wreden), *Aspergillus niger* sive *nigricans* (van Tieghem, Wreden, Wilhelm), *Aspergillus nidulans* (Eidam), *Eurotium malignum* (Lindt), *Mucor corymbifer*, and *Trichothecium roseum*; and, so far as is known, these are the same species which occasionally occur in the respiratory apparatus.

In most cases the kind of mould-fungus cannot be immediately determined; it is first necessary to make cultures of the fungus upon suitable nutrient media—such, for example, as a decoction of bread, or an infusion of bread with agar-agar, potatoes, gelatin, etc. On these the conidia which are sown grow out to germinal tubes, and form simple or branching unicellular or multicellular threads on which the peculiarly constructed fruit-bearers characteristic of the species arise and eventually produce conidia. Many form spores by copulation of cells of mycelia, and this happens especially when the supply of oxygen is lessened (Brefeld, Siebenmann).

In the mucor varieties there appear special *fruit-bearers* which differ in the different species—at one time having a single stem, at another being branched (Fig. 389, *c*)—and on the ends of which button-like swellings develop. It is from these knob-like ends that *sporangia* (*d*)—i.e., globular vesicles filled with conidia spores—grow.

Mucor corymbifer, for example, forms branching fruit-bearers (Fig. 387, *c*). The sporangia on the ends possess a smooth membrane and inclose at the time of ripening yellowish conidia spores.

The aspergilli form *conidia-bearers* which swell out spherically above and then produce numerous *sterigmata*—i.e., pedicle-like outgrowths, radially arranged, thickly crowded, shooting out from the upper half of the sphere. Each sterigma subsequently has at its end a *chain of conidia spores* (Fig. 390, *a*, *b*), which owe their formation to a constricting process.

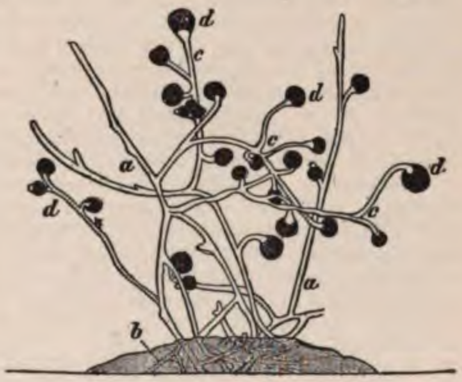

FIG. 389.—*Mucor corymbifer* in fructification. *a*, Aërial hyphæ; *b*, Mycelium lying within the nutrient gelatin; *c*, Branching fruit-bearers; *d*, Sporangia. (Preparation from a culture made on a glass slide. Magnified 100 diameters.)

The *botanical position of the aphthæ-fungus* is still doubtful. Formerly it was called *Oïdium albicans*, and reckoned, consequently, with the family Oïdium, which occurs, in different species, upon organic substances in the form of downy coatings. When cultivated from conidia it produces hyphæ, which become jointed and form conidia by transverse division of the threads, but form no peculiar fruit-bearers.

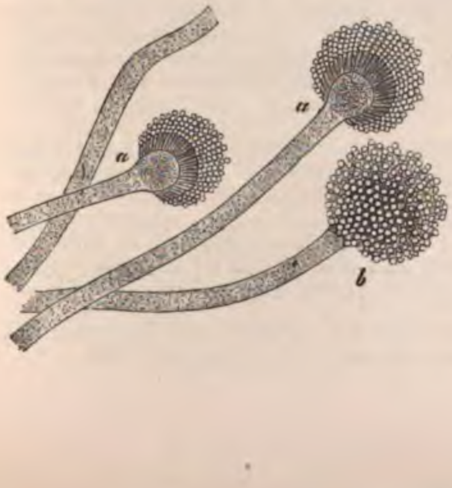

FIG. 390.—Hyphæ of *Aspergillus fumigatus*, with conidia-bearers. *a*, Fruit-heads in optical cross-section; *b*, Fruit-heads seen from above. (Magnified 300 diameters.)

According to Rees, Grawitz, and Kehrer, the aphthæ-fungus grows by budding and by the growing out of mycelia and conidia, which in turn produce at their ends, by a process of constriction, new conidia, in a manner similar to that which takes place in the yeast-fungi which belong among the mould-fungi. Consequently this fungus should be termed *Mycoderma albicans.* Linossier and Roux are, however, of the opinion that the aphthæ-fungus does not belong at all to the saccharomycetes and they regard its proper classification at present as impossible.

According to Plaut, it is identical with a mould-fungus (*Monilia candida*) which very frequently appears in nature. Kehrer suspects that it is a species of a higher fungus that has become degenerated by parasitism.

According to Neumayer,* all kinds of yeasts are able to resist the effects of the digestive juices and can travel through the intestinal canal of human beings without being killed. Unless some fermentable substance is introduced at the same time they are entirely harmless. They only exert some action on the intestinal canal when fermentable substances are introduced along with them, and then abnormal products of fermentation result which act as an irritant on the intestinal canal.

Aspergillus fumigatus, A. flavescens, A. nidulans, Eurotium malignum, Mucor rhizopodiformis, M. corymbifer, M. pusillus, and *M. ramosus* flourish at body-temperature, and, according to the investigations of Koch, Löffler, Lichtheim, Hückel, and Lindt, when the conidia of these are put into the blood-current of animals they grow out in the tissues and form hyphæ. But there is no new production of conidia, and consequently no progressive infection of the animal extending beyond the area within which the spores have been introduced. Conidia of *Mucor rhizopodiformis* and *Mucor corymbifer*, when introduced into the blood-current of rabbits, grow mainly in the kidneys and in the lymphatic apparatus of the intestines, where they cause hæmorrhagic inflammation.

Aspergillus mycoses of the respiratory apparatus are not rare in animals, especially birds, and the growth of the mycelium causes necrosis of the tissue and inflammation. According to Chantemesse, *Aspergillus fumigatus* causes in doves a disease of the mouth, lungs, liver, and kidney. The two former affections are not unlike diphtheria, while the two latter closely resemble tuberculosis, and may consequently be called *pseudotuberculosis aspergillina.* According to Potain, the infection may be transferred to man and cause ulcerative disease of the lung.

Eurotium and Aspergillus, according to Siebenmann, are two different families, having, however, very great similarity with each other, since both the mycelium and the conidia-bearers are similarly formed. The main differences between the two consist in that Eurotium produces perithecia in the form of glistening, light-yellow or sulphur-yellow, translucent bodies the size of a grain of sand, that are delicate and easily crushed. These develop continuously until completely mature spores, capable of germination, are formed. On the other hand, the genuine Aspergillus forms a hard, woody sclerotium usually embedded in a thick white matted mass of mycelia. The development of these takes place in two periods. The second part of the development takes place only when the sclerotium finds a lodgment upon a moist substratum (van Tieghem, Siebenmann).

Aspergillus flavus of Brefeld (*Eurotium aspergillus flavus* of de Bary) forms golden-yellow, greenish, and brown growths; the fruit-heads are round, yellow or olive green or brown; conidia round, seldom oval, sulphur yellow to brown, with minute warts on the surface; diameter 5 to 7 μ. *Aspergillus fumigatus* of Fresen (*Aspergillus nigrescens* of Robin) forms greenish or bluish or gray growths; the fruit-heads are long and shaped like an inverted tenpin; the conidia are round, seldom oval, smooth, mostly clear and colorless; diameter 2.5 to 3 μ. *Aspergillus niger* of van Tieghem (*Eurotium aspergillus niger* of de Bary) forms dark chocolate-brown growths; the conidia are round, brownish black or grayish brown when ripe, surface smooth or with warty thickenings; diameter 3.6 to 5 μ.

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* "Untersuchungen über die Wirkung der verschiedenen Hefearten auf den thierischen und menschlichen Organismus," *Arch. f. Hyg.*, xii., 1892.

Aspergillus can develop upon the injured sclera and bring about purulent inflammation. Leber[*] cultivated it upon the sclera and in the anterior chamber of the eye of rabbits. Finally, aspergillus also appears in the pelvis of the kidney. Babes[†] found conidia and hyphæ of a thread-fungus in ulcers of the skin which were covered by scabs, and gave to it the name *Oïdium subtile cutis.*

§ 195. **Thread-fungi** are to be regarded as **causes of disease** in a few affections of the skin; that is, in *favus, herpes tonsurans, pityriasis versicolor, sycosis parasitaria,* and in *onychomycosis.* In all of these diseases the epithelial parts of the skin contain colonizations of hyphæ and conidia, and there remains no doubt that their presence causes to some extent hyperplasia and inflammation.

The **fungus of favus** (Fig. 385) is usually called **Achorion Schönleini;** it was discovered by Schönlein in the year 1839.

Favus (*tinea favosa, scall*) has its habitat especially in the hairy portions of the skin of the head, more seldom on other parts—for example, in the substance of the nails. It is characterized by the formation of disks (*favus scutula*), varying in size from that of a lentil to that of a nickel, is sulphur yellow, and indented and pierced by a hair. In an abortive course it may merely form scales, like herpes.

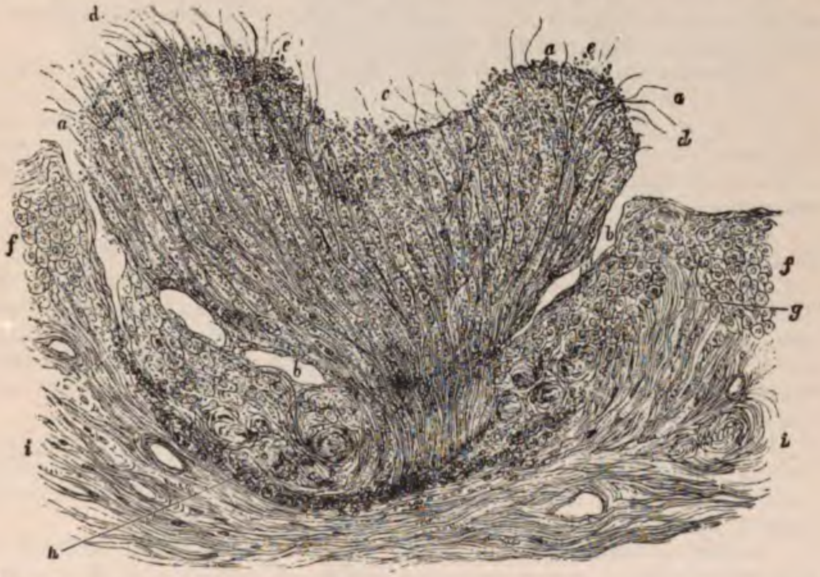

FIG. 391.—Favus scutulum. *a*, Free border of the scutulum; *b*, Dead, horny layer; *c*, *d*, Mycelial threads; *e*, Conidia; *f*, Epithelium; *g*, Papilla of the skin; *h*, Cellular infiltration at the basis of the scutulum; *i*, Cutis. (After Neumann.)

According to Kaposi, the favus scutulum originates as a small punctiform yellow focus lying under the epidermis and penetrated by a hair. It grows to the size of a lentil, and forms then a sulphur-yellow, dimpled disk showing through the upper skin. The scutulum (Fig. 391) consists of fungus threads and conidia spores and lies in a shallow funnel-shaped depression in the skin under the horny layer of the epidermis, which is drawn apart (this does not appear in the drawing). If the mass is removed during life the cavity shows a red watery surface. The favus itself forms a white, only slightly coherent mass which can be easily disintegrated in water.

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[*] *Gräfe's Archiv*, xxv.

[†] *Biol. Centralbl.*, ii., No. 8.

If the scutula are not removed they join together and form large masses. If the epidermis layer is desquamated the favus-mass becomes free and dries up to yellowish-white, mortar-like masses. The hairs appear lustreless, as if dusty, and are easy to pull out, since the fungus mycelia and conidia penetrate into the hair-shaft and into the bulb (Fig. 392, *a*), as well as into the follicle (*b*).

Not only can the hair be made to fall out by the growth of the mass of fungi, but the papilla may undergo atrophy under the pressure of the accumulation of the mass of fungi. Simultaneously a more or less intense inflammation appears in the neighborhood of the hair-follicle, and this inflammation may assume the character of an eczema.

If achorion colonizes upon a nail (*onychomycosis favosa*) it forms sulphur-yellow deposits or uniform thickening, with simultaneous loosening and cheesy degeneration of the parenchyma of the nail.

Trichophyton tonsurans, the fungus of **herpes tonsurans,** consists of long, narrow threads, but little branching and with few conidia; it forms no scutulous nodules, but penetrates easily into the hair-shaft and makes the hair brittle. According to whether the herpes develops upon hairy surfaces or upon surfaces devoid of hair, it shows certain differences.

Herpes tonsurans capillitii forms bare disks which vary in size from that of a five-cent piece to that of a silver dollar. These spots, in which the hair is broken off short, look like places where the hair has been badly cut. The surface of the skin at these spots is smooth or covered with scales and reddened on the border of the disk. If the fungus threads penetrate into the hair-follicle, pustules and scales are formed. Such disks may appear at various places and constantly increase until finally a cure takes place.

On places devoid of hair herpes forms vesicles (*herpes tonsurans vesiculosus*), and red scaly spots, disks, and circles (*herpes tonsurans squamosus*). Occasionally there appear red spots in a number of places, which rapidly spread and just as rapidly heal up.

In herpes tonsurans squamosus the fungus is found between the uppermost layers of the nucleated epidermis, close under the layer of horny cells (Kaposi).

If trichophyton develops in the nails, the nail becomes cloudy, scales off, and becomes brittle—an affection designated as *onychomycosis tonsurans.*

Sycosis parasitaria results from the fact that the development of the fungus is accompanied by an inflammation of the hairy parts of the skin, which is more severe than usual, and which leads to infiltration and suppuration—that is to say, the formation of pustules, abscesses, and papillary hyperplasia. According to Kaposi, *eczema marginatum* is also caused by the trichophyton tonsurans. It occurs especially in those places where two surfaces of skin come in contact and the skin is macerated by sweat. It is characterized by the formation of vesicles and scabs situated on the periphery of a pigmented surface. According to others (Pick, von Hebra), the fungus elements contained in the efflorescences are smaller, and are therefore called *microsporon minutissimum*. On the other hand, according to H. von Hebra, *impetigo contagiosa*, an exanthema characterized by pustules, is caused by trichophyton tonsurans.

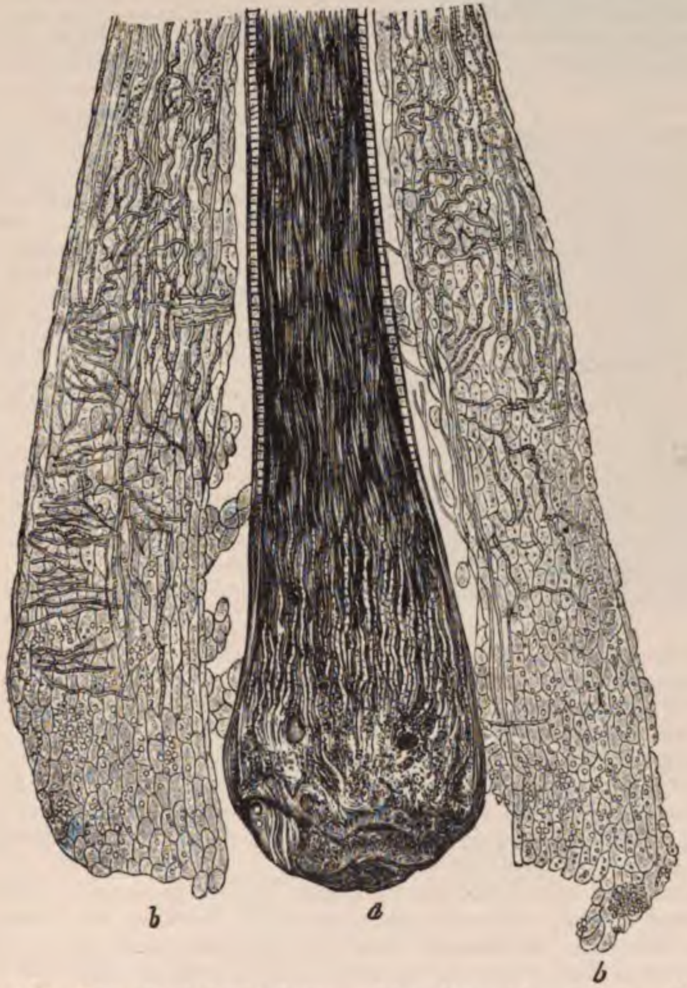

FIG. 392.—Hair affected with favus. (After Kaposi.) *a*, Bulb and shaft of the hair; *b*, Sheath of the hair-root traversed in all directions by the mycelia and conidia.

Microsporon furfur, the fungus of **pityriasis versicolor** or **dermatomycosis furfuracea**, occurs likewise in the form of threads and conidia, which are somewhat smaller than those of other skin-fungi. The alterations caused by this fungus consist of discolorations of the skin of different sizes and shapes; some of the spots being mere points, while others may be as large as the palm of the hand. These spots, which sometimes are smooth and glistening, and at other times dull and desquamating, are spread uniformly over large areas of skin. Their color varies from a pale yellow to a dark brown or a brownish red. They are found principally upon the trunk, neck, and flexor surfaces of the extremities, never on the hands, feet, or on the face.

According to investigations of Quincke, Grawitz, Boer, Nauwerck, Elsenberg, Munnich, Pick, Kral, Plaut, Biro, Sabouraud, Rosenbach, and others, the thread-fungi occurring in the diseased skin may be cultivated upon suitable nutrient media, such as agar-agar, glycerin-agar, gelatin, potatoes, blood-serum, etc.; and from the conidia simple or branching threads grow out, which become jointed (Fig. 393, *a*) and form chains of short threads (*b*). Club-shaped forms which often appear in cultures on the ends of the threads are interpreted as imperfect sporangia by Quincke and Elsenberg. The botanical position of these fungi is still undetermined. Nothing certain is known about their distribution outside the human body and the bodies of animals.

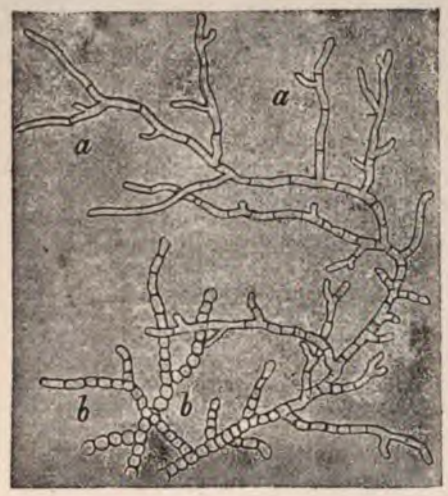

FIG. 393.—Culture of *Trichophyton tonsurans*. (From a culture obtained by Nauwerck in a hanging drop of meat-broth.) *a*, Branching threads with long joints which have delicate walls; *b*, Threads with thick-walled, short joints, some of them spherical. (Magnified 300 diameters.)

According to Quincke, three forms of fungus occur in favus-masses. Two of these represent varieties of one species of fungus. Elsenberg found only two forms, which he regards as varieties of one species. Pick, Plaut, and Biro hold fast to the etiological unity of the different forms of favus.

Sabouraud advocates the view that the fungi causing trichophytia represent entirely different varieties, which, however, all belong to the genus Botrytis. Rosenbach, who recently examined the mould-fungi occurring in deep suppurating inflammations of the skin, differentiates several trichophyton-fungi as the cause of this disease.

From the large number of investigations of various authors carried out recently it is impossible to deduce anything with certainty about the number of kinds of favus- and trichophyton-fungi. Still this much is evident from the investigations: that the character of the nutrient medium has great influence on the kind of growth, and that the difference in the results is to be attributed in large measure to the difference in the nutrient media on which the fungi were cultivated.

Inoculations with the fungi taken from cultures into the skin of human beings, rabbits, mice, etc., which were made by Grawitz, Boer, Munnich, and others, gave partly positive, partly negative results. According to Plaut, the inoculation never gives positive results when spore-formation has already taken place in the cultures.

A form of skin disease is described as *pityriasis rosea* (Gilbert) or *pityriasis maculata* and *circinnata* (Bazin), which is very similar to herpes tonsurans, and, as it seems, is caused in part by a hyphomyceta. According to Behrend,[*] who suggests the name *roseola furfuracea herpetiformis*, the disease is characterized by the appearance of prominent spots of a rose-red color, which vary in size from that of a pin's head to that of a pea or bean, and which are covered with dust-like epidermis scales. They appear oftenest on the neck and spread thence quickly over the body, but leave the head, the hands, and the feet free. The spots vanish again in two or three days. In some cases the scales contain conidia and fine mycelia threads.

Von Bärensprung[†] described an affection of the skin which is confined to the inguinal and axillary region, as *erythrasma*. It occurs in the form of rounded, sharply bordered, red-brown or pale reddish-yellow spots which are covered with dry bran-like scales. The scales contain pale, stiff, narrow, unbranched threads with one or more joints, as well as small staves and clumps of granules.[‡]

Von Hebra[§] described a peculiar itching dermatosis as *dermatomycosis diffusa flexorum*. It occurs on the elbow and bend of the knee, and is said to be caused by fungus elements which are like those of pityriasis versicolor.

Bizzozero[‖] and Bordoni-Uffreduzzi[¶] published a communication on microphyta which occur on the normal skin.

On *Madura foot* cf. § 189.

Favus and *herpes tonsurans* also occur in *domestic animals*,[**] the latter in cattle.

In invertebrate animals diseases occur not infrequently which are caused by mycelium-fungi. Thus *Botrytis Bassiana* causes the so-called *muscardine* in silkworms. *Cordyceps militaris* destroys the injurious pine-spider *Gœstropacha pini*. *Tarichium megaspermum*, a black-colored fungus, kills the destructive earth-caterpillar *Agrotis segetum*. Fungi belonging to the family *Empusa* attack especially the caterpillars of the cabbage-butterfly (*Empusa radicans*) and the house-fly (*Empusa muscæ*), and grow all through them and cause them to die. *Achyla prolifera*, according to Harz,[††] grows through the musculature of the crabs, and is the cause of the crab-pest.

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[*] *Berliner klin. Wochensch.*, 1881, Nos. 38 and 39; 1882, No. 34.

[†] *Annal. der Charité*, x., 1862.

[‡] Weyl, "Ziemssen's Handb.," xiv.

[§] *Wiener med. Blätter*, 1881; and "Die krankh. Veränder. d. Haut," Braunschweig, 1881.

[‖] *Virchow's Arch.*, 84. Bd.

[¶] *Fortschritte d. Med.*, iv., 1886.

[**] Cf. Friedberger and Fröhner, "Lehrb. d. spec. Pathol. der Hausthiere."

[††] *Jahresber. der Münchener Thierarzneischule*, 1882–1883.

SECTION XI.

The Animal Parasites.

I. Arthropoda.

1. *Arachnida.*

§ 196. The parasites included among the Arachnida are for the most part epizoa, which either temporarily or permanently inhabit the skin. But one species—the Pentastomata—occurs as larvæ within the tissues. Most of them belong to the group of *mites* (*Acaridæ*). The Pentastomata belong to the class *tongue-worms* (*Pentastomidæ* or *Linguatulidæ*).

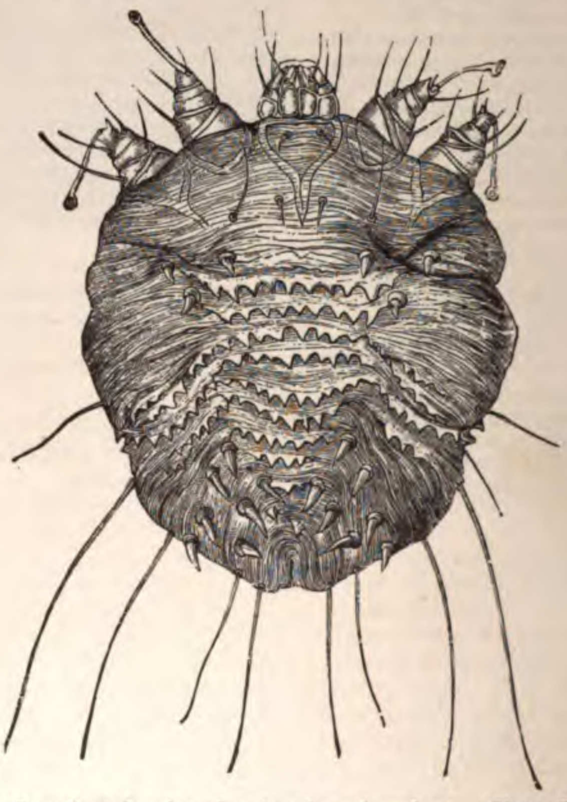

FIG. 394.—Female itch-mite, showing dorsal surface. (From Hebra's "Atlas of Skin Diseases." Magnified about 200 diameters.)

1. **Acarus scabiei,** or **Sarcoptes hominis,** the **itch-mite,** is a parasite the size of a pinhead, with a body shaped like a turtle's, provided on the ventral surface both anteriorly and posteriorly with two pairs of legs, each of which is furnished with bristles (Fig. 394). The foremost pair of legs extend out into stalk-like processes, ending in disks for clinging purposes. The same arrangement is found in the hindermost pair in the male, while the next to the last pair in the male and the last two pairs in the female end each in a long bristle. On the border of the hinder part of the body are located several bristles, while the back is covered with tooth-like knobs (Fig. 394). The head is rather round and likewise covered with bristles. The female is almost twice as large as the male.

Fig. 395.

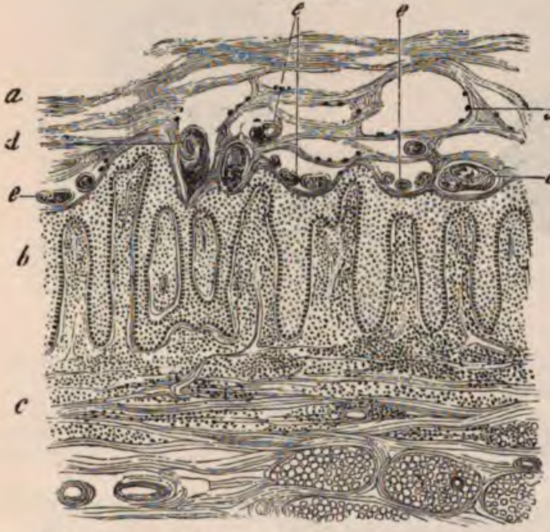

Fig. 396.

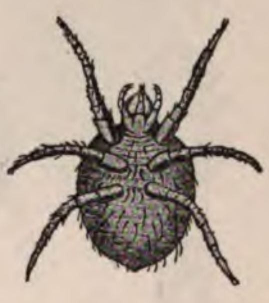

FIG. 396.—*Leptus autumnalis.* (After Küchenmeister and Zürn.)

FIG. 395.—Scabies. *a*, Horny layer of the epidermis, perforated by numerous burrows of itch-mite; *b*, Mucous layer and papillary body, the latter greatly enlarged and infiltrated with cells; *c*, Cell-infiltrated cutis; *d*, Section through a fully developed itch-mite; *e*, Eggs and embryos of various sizes; *f*, Fæces. (Preparation stained with carmine and magnified 20 diameters.)

The mite dwells in the epidermal layer of the skin (Fig. 395, *a*, *d*), in which it digs burrows, some of which are 10 cm. in length. In these burrows the female (*d*) lays her eggs, which develop *in situ* into young itch-mites (*e*). These bury themselves still deeper in the epidermis, and after several times shedding their skins, develop into sexually mature individuals. The skin responds to the irritation which the presence of the mites occasions, by increased epithelial cell-production (*a*) and by inflammation (*c*). The latter is considerably increased by scratching the spots which itch in consequence of the invasion.

2. **Leptus autumnalis,** the *harvest-mite* (Fig. 396), is the red-colored larva of a variety of Trombidæ, which lives upon grass and bushes and upon grain, and when opportunity offers alights upon the human skin; here it bores its way into the epithelium and occasions itching and inflammation.

3. **Demodex** or **Acarus folliculorum hominis** (Fig. 397) occurs at times singly or in groups in the sebum of the hair-follicles and the ducts of the sebaceous glands. It is in the neighborhood of 0.3 mm. long, and has on its anterior ventral surface four pairs of short, thick legs. The head is furnished with a snout and two feelers.

4. **Ixodes ricinus**, the *wood-jack* or *wood-tick* (Fig. 398), is a fairly large yellowish-brown member of the Arachnida, belonging to the group of ticks. It has a black head provided with a sucking apparatus, and a very distensible leathery body. It commonly occurs upon grass and bushes, and sometimes alights upon man or beast. By means of its sucking apparatus it draws blood from the skin, and in this way swells up to a very remarkable extent.

Fig. 397.

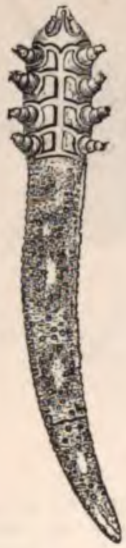

Fig. 398.

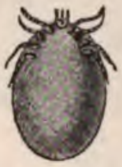

Fig. 399.

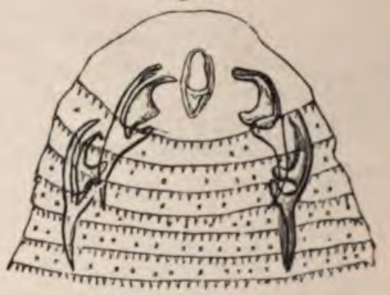

FIG. 397.—*Acarus folliculorum hominis.* (After Perls. Magnified 300 diameters.)

FIG. 398.—*Ixodes ricinus*, sucked half full of blood. (Magnified 2 diameters.)

FIG. 399.—Head end of *Pentastoma denticulatum.* (After Perls. Magnified 40 diameters.)

5. **Pentastoma denticulatum** is the larva of **Pentastoma tænioides**, a lance-shaped organism belonging to the order of the tongue-worms or Pentastomidæ. It inhabits the nasal, frontal, and maxillary sinuses of various animals, especially the dog. It very seldom occurs in human beings (Laudon), and when it does it occasions inflammations. The sexually mature female is from 60 to 130 mm. long and anteriorly from 8 to 10 mm. broad, while the male measures from 16 to 20 mm. in length and anteriorly from 3 to 4 mm. in breadth. The larva is from 4 to 5 mm. long and 1.5 mm. wide; is plump, and of somewhat flattened spherical shape. Its location is usually the liver or spleen, and, more rarely, other organs of men and herbivora. It is a quite common, though not a dangerous, parasite. Its body is divided off into some ninety ring-shaped segments, which are provided around the borders with thorn-like processes, while the head extremity is furnished with four hook-shaped feet.

Living mites occur very frequently among the *domestic animals* as parasites on the skin, representing various species of different families.

Sarcoptes hominis, the burrow- or itch-mite of man, occurs also in horses and Neapolitan sheep. Not only this, but various kinds of sarcoptes are distinguishable, which infest the domestic animals—for instance, *Sarcoptes squamiferus*, occurring in dogs, swine, sheep, and goats, and *Sarcoptes minor*, in cats and rabbits.

Dermatophagus, the *biting-mite* (Fig. 400), with broad head, occurs in different animals, and various species of the same are distinguished. They live upon the cells of the epidermis and occasion desquamation of the skin.

Fig. 400.

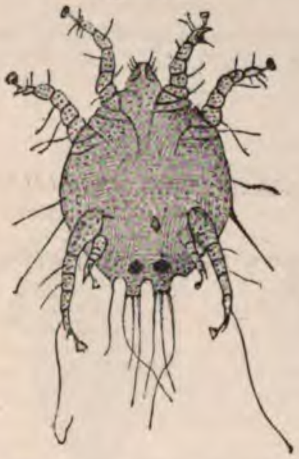

Fig. 401.

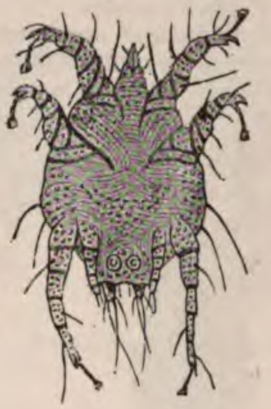

FIG. 400.—Male of the *Dermatophagus communis*, showing ventral surface. (After Pütz. Magnified 50 diameters.)

FIG. 401.—Male of the *Dermatocoptes communis*, showing ventral surface. (After Pütz. Magnified 50 diameters.)

Dermatocoptes, the *sucking-mite* (Fig. 401), with long slender head, robs the skin of blood and lymph, and produces inflammation. *Dermatocoptes communis* occurs in horses, cattle, and sheep. *Dermatocoptes cuniculi* is a parasite infesting the ears of rabbits.

Symbiotes equi of Gerlach is a mite occurring chiefly on the feet of heavy English and Scotch horses, where it excites a moist dermatitis, often incorrectly called *malanders*.

Dermanyssus avium is a red blood-sucking mite about 1 mm. long, which is seen often in birds.

Of the Tick family there occur in dogs, cattle, and sheep *various kinds of Ixodes*, while in pigeons the *Argas reflexus* and others are found.

Leptus autumnalis occurs also in dogs and chickens.

Species of Demodex occur in dogs and swine, occasioning pustular eruptions.

Pentastomata are found also in cattle, sheep, and goats, and in certain regions are abundant in cattle.

2. *Insects.*

§ 197. Most of the parasitic insects are epizoa. Part of them remain only temporarily upon the skin, and from it derive their nourishment, while others remain there permanently and utilize the skin structures as a place in which to deposit their eggs. The following may be mentioned as belonging to the numerous species here included:

1. **Pediculus capitis,** the *head-louse* (Fig. 402), occupies the hairy scalp, and derives its nourishment (i.e., blood) from the skin by means of its feeding apparatus. Its eggs or nits are barrel-shaped and white, and are fastened to the hairs by a coating of chitin. It takes the embryo only about eight days to hatch out. In consequence of the scratching induced by the itching there arise frequently quite severe dermatites, especially eczema.

2. **Pediculus pubis,** the *felt-* or *crab-louse* (Fig. 403), dwells in the hairy parts of the trunk and extremities. Its habits are the same as those of the *Pediculus capitis.*

3. **Pediculus vestimentorum,** the *clothing-* or *body-louse* (Fig. 404), lives in the wearing-apparel and deposits its eggs there as well. It gets upon man to obtain nourishment.

Fig. 402.

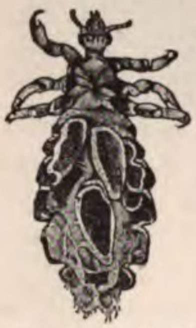

Fig. 403.

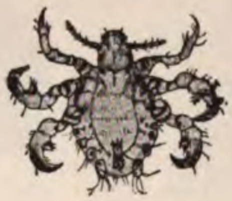

Fig. 404.

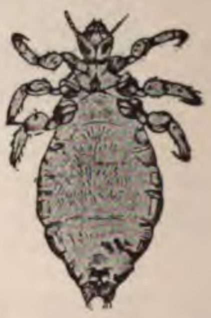

FIG. 402.—Female *Pediculus capitis*, showing ventral surface. (Küchenmeister and Zürn. Magnified 13 diameters.)

FIG. 403.—Male *Pediculus pubis*, showing ventral surface. (Küchenmeister and Zürn. Magnified 13 diameters.)

Fig. 404.—Female *Pediculus vestimentorum*, showing ventral surface. (Küchenmeister and Zürn. Magnified 9 diameters.)

4. **Cimex lectuarius,** the *bedbug,* dwells in beds, floors, closets, etc., and gets upon people at night to suck blood. It causes wheals upon the skin.

5. **Pulex irritans,** the *common flea,* also draws blood from the skin. A little hæmorrhagic dot may be found where it has sucked. Sometimes, also, there appear local swellings and wheals. It lays its eggs in the cracks of floors, in sawdust, etc.

6. **Pulex penetrans,** the *sand-flea,* occurs in South Africa in the sand. The female lays her eggs in the skin and causes thereby intense inflammation.

7. **Gnats,** having mouths provided with stinging and sucking apparatus (*Culicidæ* and *Tipulidæ*), **horse-flies** (*Tabanidæ*), and **common flies** (*Stomoxyidæ*) draw blood frequently from the human skin. Various flies (Œstridæ, Musca, Lucilia, Sarcophaga) occasionally lay their eggs in wounds or in the cavities of the body accessible to them, after which the developing mites fasten themselves on the affected places (*myiasis*). Under certain circumstances their larvæ may also get into the intestinal

tract with the food, and here develop further. This happens especially when abnormal conditions exist in stomach and bowel which interfere with digestion.

There occurs in South America a fly, the *Musca anthropophaga*, whose larvæ infest the nasal and frontal sinuses, the pharynx and larynx of man, and produce inflammation.*

Dermatolia noxialis, a horse-fly of Central America, deposits its eggs on the skin of man and beast. The larvæ, as they hatch out, bore deeply into the skin and cause painful swellings.

The parasites belonging to the family of *Muscidæ* play a much more important rôle in the domestic animals than in man, and it is especially the *species of Œstrus* whose larvæ infest animals. Thus, for example, the larvæ of the *Gastrophilus equi* (Fig. 405), *Gastrophilus pecorum*, and *Gastrophilus hæmorrhoidalis* live in the stomach and adjacent section of the intestine of the horse, and here they complete their development until they reach the chrysalis stage, upon which they depart.

Œstrus ovis lays its larvæ in the nasal cavities of the sheep, from whence they wander into the frontal, nasal, and maxillary cavities, and under certain circumstances also into the cranial cavity, and occasion inflammation.

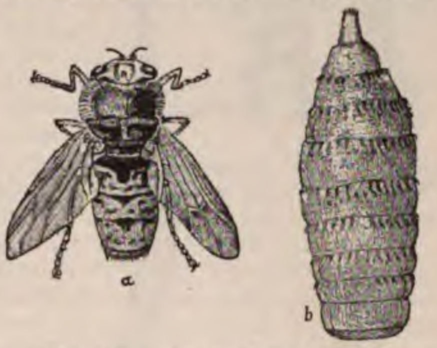

FIG. 405.—*Gastrophilus equi.* (After Brauer.) *a*, Male; *b*, Larva.

The larva of the *Œstrus bovis* bores into the skin of the cow, and here develops as far as the chrysalis stage, when it again leaves its host.

II. Vermes (Worms).

1. *Nematodes* (*Roundworms*).

§ 198. All the **roundworms** which occur as parasites belong to the **Nematodes.** They possess a slender, cylindrical, extended, and sometimes filiform body, with neither segments nor appendages. The cuticle is thick and elastic. The oral opening is found at one extremity, and is provided sometimes with soft and sometimes with horn-like lips. The elongated gut, together with the pharynx and chyle-stomach, extends through the entire body-cavity (Fig. 406), opening upon the ventral aspect a short distance from the usually awl-shaped posterior extremity. The sexual organs and their openings are also found on the ventral surface. The female sexual orifice occurs at about the middle of the body, less frequently near the anterior or posterior extremity (Fig. 406, A, *a*). In the male the sexual orifice and the anus are located together (B, *c*). The chitinous covering of the lower gut forms in the male the means of clinging in the act of copulation. The males are usually smaller than the females. The development is continuous, and the metamorphoses are not striking. The nematodes which occur in man are, some of them, harmless intestinal parasites, while others are very dangerous, sometimes even fatal, parasites of various organs.

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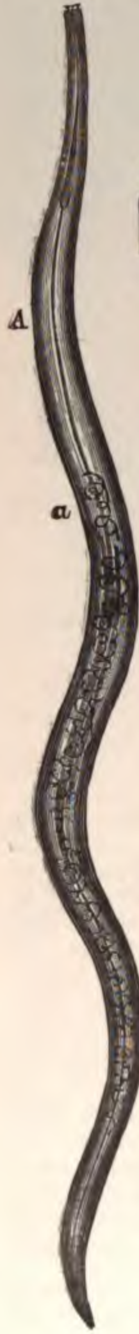
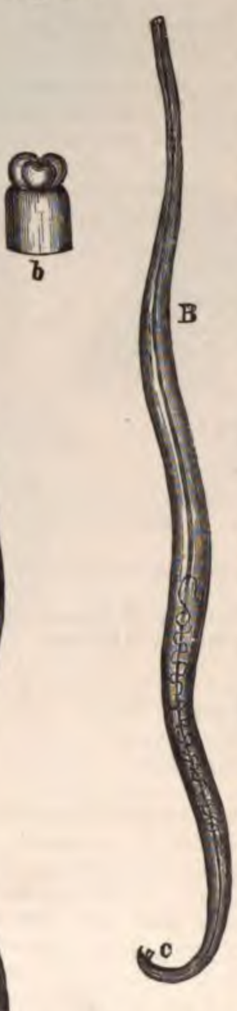
* Conèl, *Annales d. Sc. nat. Zoöl.*, tome x., 1878.

§ 199. **Ascaris lumbricoides**, the *common spool-* or *roundworm* (Fig. 406), is a light-brown or reddish-colored worm cylindrical in shape, and tapering generally to a point at the end. The female (A) is from 25 to 40 cm. long, the male (B) considerably smaller, and the posterior extremity of the latter is bent in the form of a hook and provided with two spicules (*c*) or chitin processes.

Fig. 406.





The mouth (*b*) is inclosed by three muscular lips, provided with very fine teeth. The sexual opening of the female (A, *a*) lies anterior to the middle of the body. The eggs, which the mature female contains in enormous numbers, possess in their fully developed condition a double shell (Fig. 407), and around this is an albuminous envelope. Their size amounts to between 50 and 60 μ. The worm inhabits the entire intestinal canal, but most frequently the small intestine. It is the most common parasite in man, and frequently is found in great numbers. When mature females are present, the fæces contain numerous eggs. These are very resistant to external influences—for example, drying and freezing.

The eggs require no intermediate host (Lutz, Leuckart, Grassi, Eppstein) in order to develop into the roundworm, so that a person may become infected by swallowing the eggs which have been expelled from the bowel and have matured in the fæces. According to culture experiments which Eppstein carried out on human beings with eggs which had long been cultivated on damp fæces, the roundworm attains sexual maturity in from ten to twelve weeks after ingestion of the eggs. At this time the male is from 13 to 15 cm. long, and the female from 20 to 30 cm. Its presence in the intestine does not usually cause any noticeable disturbance. Only when present in large numbers does it sometimes, especially

Fig. 407.

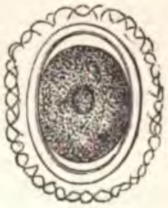


FIG. 406.—*Ascaris lumbricoides*. (After Perls.) A, Female; B, Male. (Natural size.) At *a* is the female sexual orifice; *c*, The two spicules of the male; *b*, Head extremity (magnified) of the worm, with the three lips.

FIG. 407.—Egg of *Ascaris lumbricoides* (after Leuckart), with shell and albuminous envelope. (Magnified 300 diameters.)

in children, cause intestinal catarrh, vomiting, nervous excitability, and convulsions. Occasionally it crawls into normal or pathological openings in the wall of the intestinal canal, and in this way causes trouble. Thus, when it gets into the ductus choledochus, it may produce bile-stasis. When it penetrates through an ulcer outward into the abdominal cavity or into a hernial sac, it may occasion inflammation of that particular tissue. By Leuckart it is also said to have the power of boring through the uninjured bowel-wall. Frequently the worm passes away *per anum* with the fæces, and at times *per os* in vomiting. From the pharynx it may wander into the larynx.

A very rare intestinal parasite is the *Ascaris mystax*, the roundworm of the cat, which is very much smaller than the ordinary roundworm.

§ 200. **Oxyuris vermicularis**, the *awl-tail-*, *maggot-*, or *threadworm* (Fig. 408), is a small roundworm, the female being 10 mm. long (*a*, *b*) and pointed at the caudal end like an awl, while the male is 4 mm. long (*c*), with a blunt posterior ending provided with a spiculum.

Fig. 408.

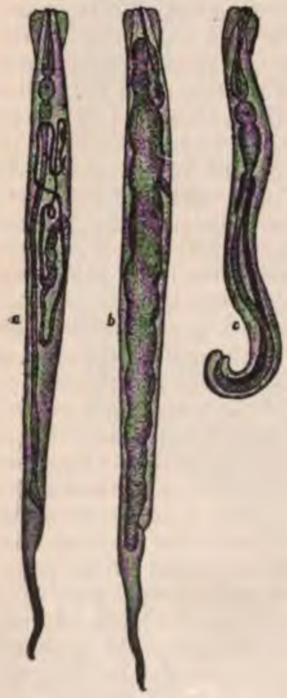


Fig. 409.

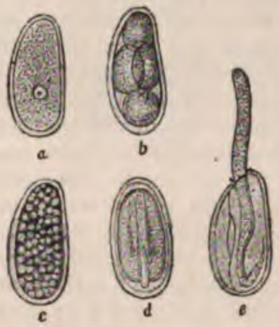


Fig. 408.—*Oxyuris vermicularis.* *a*, Sexually mature female; *b*, Female full of eggs; *c*, Male. (After Heller. Magnified 10 diameters.)

Fig. 409.—Eggs of *Oxyuris vermicularis*, in various stages of development. (After Zenker and Heller.) *a*, *b*, *c*, Segmentation of yolk; *d*, Tadpole-shaped embryo; *e*, Worm-shaped embryo. (Magnified 250 diameters.)

The eggs (Fig. 409, *a*), which the belly of the female often lodges in immense numbers, are 50 μ long and 24 μ broad, have a flat and a curved surface, and a shell which is covered by a thin albuminous layer. The *Oxyuris vermicularis* inhabits the large intestine and the lower part of the small intestine. According to Zenker and Heller, only the fructified mature female is found in the large intestine, while the younger individuals and the males occur in the small intestine. In greater or smaller numbers they are of very common occurrence. At night they are prone to wander outside the rectum into the anal region, and also enter the vagina, occasioning itching. The scratching thus produced sometimes leads to dermatitis, erections, masturbation, etc.

For the eggs to develop (Fig. 409, *a*, *b*, *c*, *d*, *e*) it is necessary after their expulsion with the fæces that they again make their way into the stomach of man or beast. It is very probable that the original possessor of the *Oxyuris vermicularis* reinfects himself, the eggs which remained stuck to his fingers when he scratched himself, later getting into his mouth.

The eggs are very resistant to drying, and when dry may be scattered from place to place.*

§ 201. **Anchylostoma duodenale** (*Dochmius duodenalis* or *Strongylus duodenalis*) is a small palisade-worm which tenants the upper part of the small intestine (Fig. 410). The cylindrical body of the female possesses a length of from 5 to 18 mm., while that of the male is from 6 to 10 mm. long. The cephalic end (Fig. 411) is curved toward the dorsal surface, and is provided with a mouth-capsule located on the ventral side (*d*). It is almost completely divided dorsally, and the cleft is covered by two chitinous layers. On the ventral border are four incurving teeth (*b*), while on the dorsal border are two teeth perpendicularly arranged (*c*), both kinds being held together by chitinous bands. In addition the interior of the capsule contains a conical elevation beneath the cleft in the dorsal surface.

The male is provided at the caudal extremity with a threefold bursa (Fig. 410, *i*) and two thin bone-like spicules (*p*). In the female the caudal end is pointed and is armed with an awl-like prong; the vulva lies back of the centre of the body. The oval eggs (Fig. 412) are from 44 to 67 μ long and from 23 to 40 μ broad. They undergo the first stages of cleavage in the human intestine (*a*, *b*, *c*, *d*), develop still further in muddy water (*e*, *f*), and may then, if brought into the intestinal canal of man, immediately develop again into sexually mature individuals. Their presence in the intestinal tract, where they occupy chiefly the duodenum and small intestine, is not without danger. With its teeth the worm works its way into the mucous membrane as far as the submucosa, and sucks itself full of blood. Its point of attack is distinguishable later by a small ecchymosis, in the centre of which lies a white spot with a central perforation. Occasionally there are found in the mucous membrane of the bowel small blood-filled holes containing each a coiled-up worm. When present in large numbers they cause continuous and serious loss of blood, which produces a profound anæmia in the patient (*Egyptian chlorosis*). Perroncito, Graziadei, and Bäumler have ascertained the presence of anchylostomata in the intestine even several years after infection has taken place. The parasite is common in the tropics. According to Griesinger and Bilharz, something like a quarter of the population of Egypt suffer from this disease. A few years ago the parasite was very frequently observed among the laborers in the St. Gotthard Tunnel. Menche and Leichtenstern state that the brick-fields of the province of the Rhine are in great part infected with anchylostomata, and that the disease which was long considered in that region as brick-burner's anæmia is caused by the Anchylostoma.

The **Eustrongylus gigas**, a palisade-worm of red color, whose female reaches a length of a metre, is a very rare parasite, which has been

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* For the literature of this subject consult Huber, "Bibliographie der klinischen Helminthologie," München, 1893.

Fig. 410.

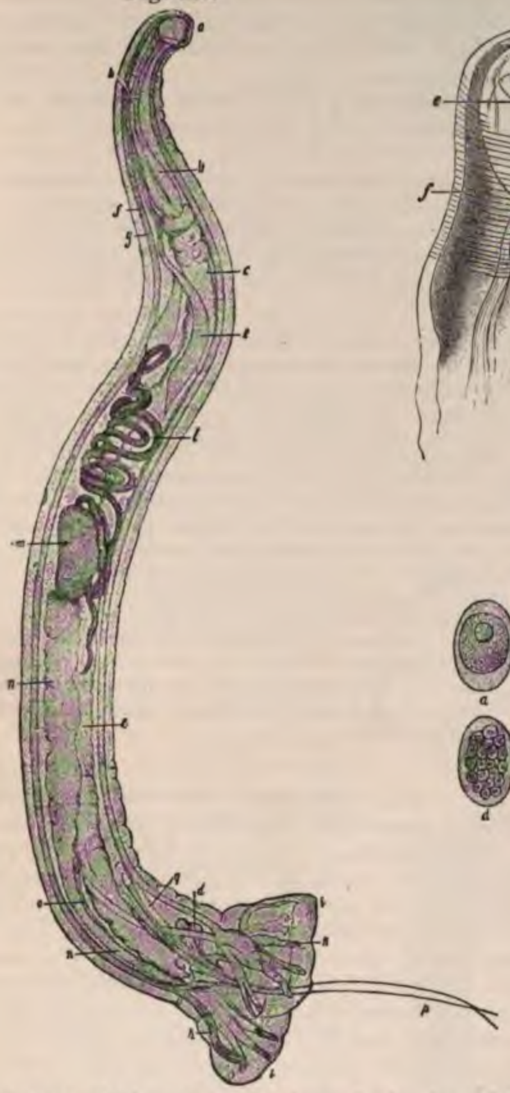

Fig. 411.

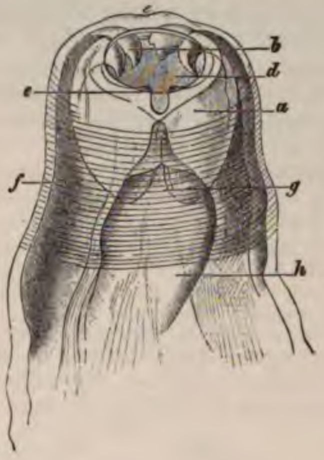

Fig. 412.

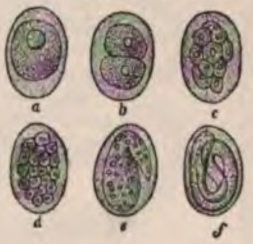

FIG. 410.—Male of *Anchylostoma duodenale.* (After Schulthess.) *a*, Head with mouth-capsule; *b*, Œsophagus; *c*, Intestine; *d*, Anal glands; *e*, Cervical glands; *f*, Skin; *g*, Muscular layer; *h*, Porus excretorius; *i*, Triple bursa; *k*, Ribs of the bursa; *l*, Testicular canal; *m*, Vesicula seminalis; *n*, Ductus ejaculatorius; *o*, Groove of latter; *p*, Penis; *q*, Sheath of penis. (Magnified 20 diameters.)

FIG. 411.—Cephalic end of *Anchylostoma duodenale.* (After Schulthess.) *a*, Mouth-capsule; *b*, Teeth of ventral border; *c*, Teeth of dorsal border; *d*, Buccal cavity; *e*, Skin-sac on ventral side of head; *f*, Muscular layer; *g*, Dorsal groove; *h*, Œsophagus.

FIG. 412.—Eggs of *Anchylostoma duodenale.* (After Perroncito and Schulthess.) *a*, *b*, *c*, *d*, Different stages of cleavage; *e*, *f*, Eggs with embryos. (Magnified 200 diameters.)

observed but a few times in the pelvis of the human kidney. It possesses a buccal opening with six papillæ, and the male has at the caudal end a bursa with a single spiculum. The eggs are oval, 0.06 mm. long, and provided with an uneven albuminous envelope.

The **Strongylus longevaginatus**, a white thread-like worm 26 mm. long, was observed in one instance in the lung of a boy.

Species of Dochmius occur also in *dogs and cats*—not only the *Dochmius duodenalis*, but also other varieties—and are said to likewise cause anæmia.

Varieties of Strongylus occur very frequently in the domestic animals, sometimes as intestinal parasites, again as dwellers in the lungs or vascular system, as well as other tissues. We have to thank A. Mueller for an excellent monograph on the Nematodes of mammalians.*

Strongylus armatus is a parasite of the horse, which enters the intestinal tract as an embryo, and thence bores into the mesenteric arteries, or even into a renal artery, where it develops to sexual maturity and then wanders back into the large intestine. The fully developed male worm is from 20 to 30 mm. long, the female from 20 to 55 mm. It causes clots to form in the arteries, and brings about aneurismal dilatations of the vessel-wall.

Strongylus filaria is a filiform worm some 25 to 84 mm. long, which occurs in the air-passages of sheep, goats, rabbits, and deer, and there occasions inflammations. *Strongylus rufescens* and *Strongylus paradoxus*, *Nematoidium ovis pulmonale* (Lydtin) or *Pseudalius ovis pulmonalis* (Koch), are likewise occupants of sheep's lungs, *Strongylus paradoxus* also of the lungs of swine. *Strongylus commutatus* occurs in the lungs of the hare and rabbit, while *Strongylus syngamus* and *Strongylus bronchialis* are found in the air-passages of birds, all three being productive of inflammation. *Strongylus micrurus* (Ströse †) occurs in cows and calves, not only in the air-passages, but also in arterial aneurisms.

§ 202. The **Anguillula stercoralis** or *Pseudorhabditis stercoralis* (Fig. 413) is a small nematode, the male possessing a length of 0.88 mm., the female 1.2 mm. The worm is indigenous to Cochin China and Italy, and in the latter country often occurs simultaneously with the Anchylostoma. The fructified female contains both eggs and embryos (Fig. 413). The latter, which at birth spread through the whole intestinal tract, the gall-ducts, and the pancreatic duct, and even, according to Normand, occasion diarrhœa, may develop inside the intestine up to the point of formation of the sexual organs (Perroncito). In all probability some even attain complete sexual maturity, while others pass away earlier with the fæces. The larvæ at their departure are from 250 to 370 μ long.

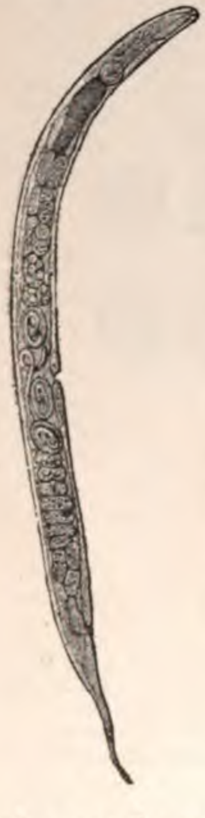

FIG. 413.—Female of *Anguillula stercoralis*, with eggs and embryos. (After Perroncito. Magnified 85 diameters.)

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* "Die Nematoden der Säugethierlungen und die Lungenwurmkrankheit, eine zoologisch-patholog. Untersuchung," *Deutsche Zeit. f. Thiermed.*, xv., 1889.

† "Bau von *Strongylus micrurus*," *Deutsche Zeitschr. f. Thiermed.*, xviii., 1892.

According to Golgi and Monti, the *Anguillula stercoralis* penetrates into Lieberkühn's crypts, where it deposits its eggs and young; these cause sometimes epithelial degeneration, and at other times epithelial hypertrophy.

The **Anguillula intestinalis** is a roundworm 2.25 mm. long, of which species the female alone is known. It has the same distribution as the *Anguillula stercoralis*. The eggs do not develop in the intestinal canal, or, at any rate, exhibit only the first stages of segmentation at the time of their departure with the fæces. At a temperature of from 25° to 30° C. there sets in a very rapid segmentation of the eggs in the diluted fæces, and the development of the embryos commences, though the latter attain their complete development only in a new host.

§ 203. **Trichocephalus dispar**, the *whip-worm*, is, indeed, a common parasite, but an entirely harmless one which is found in the cæcum and neighboring section of the intestine. Both male and female are from 4 to 5 cm. long (Fig. 414). The anterior body-cavity (*a*, *b*) is very narrow and thread-like, while the posterior half of the body, which contains the sexual organs (*f*, *g*, *l*, *o*, *p*), is very much thicker, cylindrical in the female (B), and in the male (A) coiled up and provided with a spiculum (*g*).

The eggs (Fig. 415) have an elongated oval shape, being 50 μ long. They possess a thick brown shell, which exhibits at each pole a peg-shaped swelling clear as crystal.

The first embryonal development takes place in water and damp earth. It progresses extremely slowly, requiring in the summer from four to five months, and in the colder periods of the year a much longer time. The eggs are very resistant to cold and dryness.*

Fig. 414.

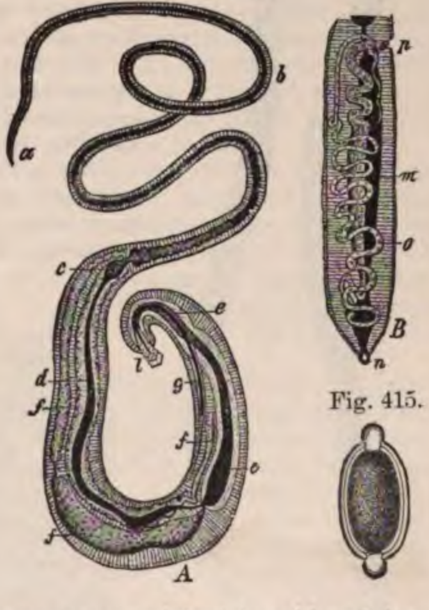

Fig. 415.

FIG. 414.—*Trichocephalus dispar*. A, Male; B, Caudal end of female. *a*, Cephalic end; *b*, Anterior belly with œsophagus; *c*, Stomach; *d*, Intestine; *e*, Cloacus; *f*, Seminal duct; *g*, Penis; *l*, Bell-shaped penis-sheath and end of penis; *m*, Intestine of female; *n*, Anus; *o*, Uterus; *p*, Vaginal orifice. (After Küchenmeister and Zürn. Magnified 10 diameters.)

FIG. 415.—Egg of *Trichocephalus dispar*. (After Heller. Magnified 350 diameters.)

Varieties of Trichocephalus occur also in the *domestic animals*.

§ 204. The **Trichina spiralis** is seen in two forms—namely, the trichina of the intestine and the trichina of the muscles.

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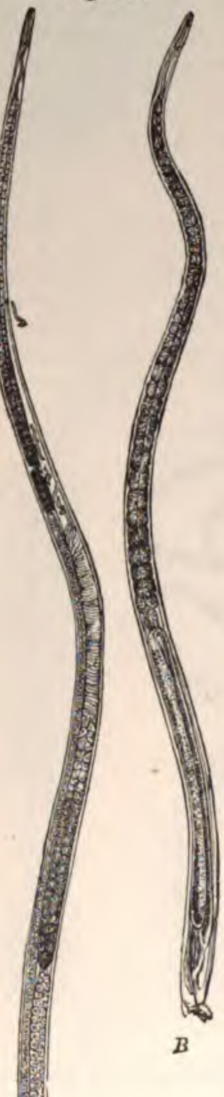
* For the literature on this subject, consult Huber, *op. cit.*

It reaches sexual maturity as an intestinal parasite (Fig. 416)—the **intestinal trichina**—and then appears as a small, white, hair-like worm, visible even to the naked eye. The female (A) is 3 mm. long, the male (B) considerably smaller. The hinder part of the body is elongated in both sexes, and in the male (B) is provided on the dorsal half with two conical-shaped terminal pegs, which are directed toward the belly, and are separated from each other by four knob-like papillæ. Instead of a spiculum, the muscular cloacus is protruded outward in copulation.

Fig. 416.



The intestinal canal begins with a muscular mouth, which has the functions and appearance of an intestine, and farther on, increasing in calibre, passes directly into the food-canal. This is surrounded throughout its entire length by so-called cell-bodies—that is, a row of large cells. The stomach, which is the continuation of the food-canal, is a flask-shaped dilatation of the intestine, and is covered with fine granular cells. The stomach passes, with no important change of structure, into the intestine, which in the male joins with the seminal duct at the caudal end to form a cloacus.

The testicle consists of a pouch, which commences near the caudal end of the body in a blind sac, proceeds forward as far as the cell-body, and bending there, passes over into the seminal duct.

The sexual organs of the female (A) consist of a single ovary, a uterus, and a vagina, which opens outward at the junction of the first and second quarters. The ovary likewise forms a pouch lo-

Fig 417.

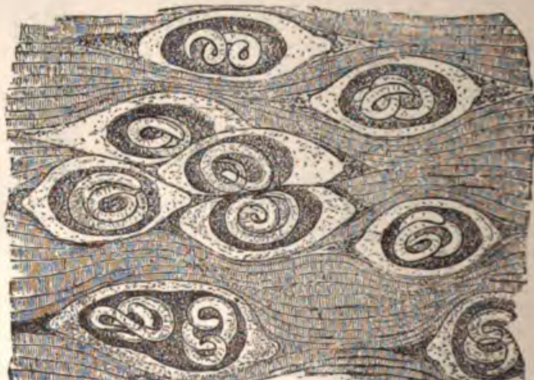


Fig. 416.—Sexually mature trichinæ. A, Female; B, Male. (After Leuckart. Magnified 120 diameters.)

Fig. 417.—Encapsulated muscle-trichinæ. (After Leuckart. Magnified 60 diameters.)

cated close to the posterior extremity of the body, and in this develop the roundish eggs. The pouch passes anteriorly into the sac-shaped uterus.

The eggs develop within the uterus into embryos which are set free at birth.

The **muscle-trichina** (Fig. 417) is a worm from 0.7 to 1.0 mm. long which lives in the muscles of the body. It is generally coiled up in a spiral, and lies in a capsule, which occasionally contains lime-salts. Between the coils of the worm is a fine granular mass.

A single capsule may contain two, three, or even five trichinæ.

If a piece of muscle which contains living trichinæ finds its way into the stomach of a host—for example, man—the capsules are dissolved and the trichinæ liberated. Sexual maturity is attained in the intestinal canal in two and a half days, when copulation occurs. On the seventh day after the introduction of the muscle-trichinæ the birth of embryos begins, and continues quite a while, apparently for weeks. A single female trichina is said to bear from one thousand to thirteen hundred young. According to the investigations of Askanazy, the female trichinæ penetrate into the intestinal villi and deposit the embryos in the lymph-vessels, whence their migration begins. How far they are swept passively along with the lymph, how far active migration is concerned in their spreading, is not yet settled. Once in the muscles, they penetrate the primitive fibres, bring their contents to degeneration and destruction, and grow in fourteen days to fully developed muscle-trichinæ. In the neighborhood of the muscle-fibres which contain trichinæ there sets in a growth of muscle-nuclei with inflammation. At first the embryo is inclosed only by the sarcolemma. Later, a capsule is formed, partly by a substance manufactured by the worm, resembling chitin, and partly through hyperplasia of the bordering connective tissue.

The intestinal trichinæ have a limited lifetime of from five to eight weeks. The muscle-trichinæ, on the other hand, may exist a very long, possibly an unlimited time (that is, until the death of the affected individual), or at any rate for years. After some time there takes place a deposition of lime-salts in the capsule, which causes it to appear glistening white by diffused light, and by transmitted light cloudy and dark. If from any cause the trichinæ die, the contents of the capsule also become calcified.

The trichinæ have been observed not only in man, but in the swine, cat, rat, mouse, marmot, polecat, fox, marten, badger, hedgehog, and raccoon. Muscle-trichinæ are also produced in rabbits, guinea-pigs, sheep, and dogs by feeding on trichina-infected meat. Human beings are infected by the ingestion of uncooked pork. The invasion of trichinæ produces various phenomena in man. The symptoms of an intestinal catarrh follow the introduction of trichinous meat into the intestine. As the trichinæ wander into the muscles there arise pains, swellings, œdema, and paralyses, and not infrequently fever sets in. The symptoms are most severe in the fourth and fifth weeks. Not infrequently death follows. The intensity and severity of the symptoms are in general proportionate to the number of invading trichinæ in the muscles.

The trichinæ are found in greatest numbers in the diaphragm, the tongue, the intercostal muscles, the muscles of the neck and larynx, and the thighs, and are scattered most sparsely in the distant muscles of the extremities. The collection is usually greatest around the attachments of the tendons.

§ 205. **Filaria** or **Dracunculus medinensis** (Fig. 418), the *guinea-worm*, is a thin, filiform worm from 60 to 100 cm. long. Up to the present the female alone is known. The cephalic end is rounded off, while the caudal end tapers into a pointed tail curved toward the belly. The external covering consists of a firm cuticle which becomes thickened at the cephalic end, taking the shape of a shield. The intestinal canal is narrow and possesses no anus. The uterus, filled with young, takes up the major part of the whole body-cavity. The embryos have no egg-shell, but possess a thick cuticle and an awl-shaped tail. As intermediate host, the embryos seek small crustacea, contained in which they reach the stomach in the drinking-water. In Africa and Asia the worm occurs very frequently. It develops in the skin to sexual maturity, and occasions cutaneous abscesses on the affected spots. Most usually it is found on the lower extremities, especially in the region of the heel.

Fig. 418.

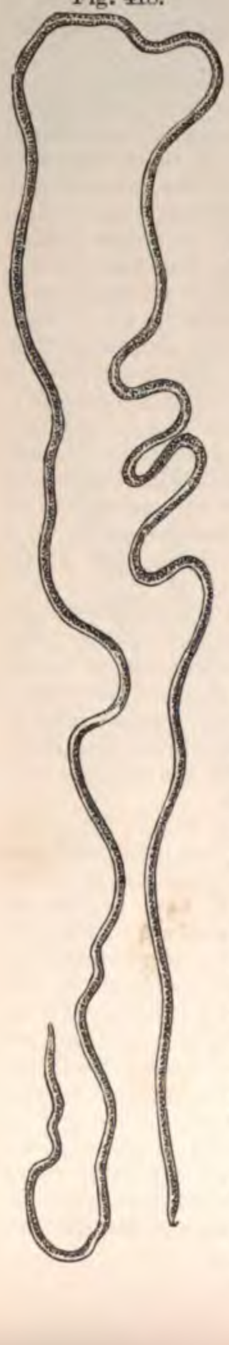
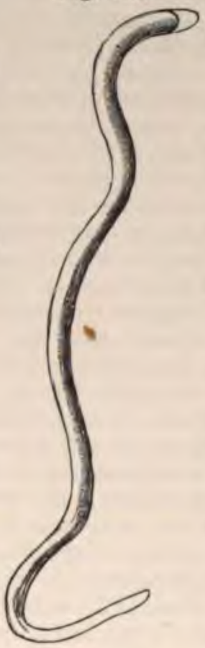


Fig. 419.



Filaria sanguinis hominis is the name applied to the larvæ of a worm which, when sexually mature, is filiform, and measures from 8 to 10 cm. in length. It is called after its discoverer **Filaria Bancrofti.** The *larvæ* are 0.35 mm. long, and occur in the blood and lymph of man. The worm lives in the lymphatics, especially those of the scrotum and lower extremities. It causes lymph-stasis and inflammations, which in turn lead to *swelling of the lymphatic glands and elephantiasis-like thickening of the tissues,* combined with œdema and lymphangiectasia. Pustular inflammations, lymph-abscesses, buboes, chylous hydrocele, and ascites may also occur in consequence of its presence.

From the lymphatics of the limbs and scrotum the eggs and embryos (0.35 mm. long) (Fig. 419) spread into other parts of the lymphatic system and into the blood, and cause hæmaturia, chyluria, and chylous diarrhœa. According to Manson and Scheube, the migration into the blood takes place chiefly

FIG. 418.—*Filaria* or *Dracunculus medinensis.* (Leuckart. Life size.)

FIG. 419.—Embryo of *Filaria Bancrofti*, known as *Filaria sanguinis hominis.* (After Lewis. Magnified 400 diameters.)

at night—that is, while the patient is at rest. The hæmaturia is the result of a collection of embryos in the blood-vessels of the urinary organs. The chyluria and the chylous diarrhœa, on the other hand, are said to come from the fact that the parasites obstruct the thoracic duct, so that lymph-stasis occurs; this affects also the lymphatics of the bladder and intestine, and permits exudation of lymph in these localities. According to Scheube, the bursting of the lymphatics lacerates the blood-vessels also, so that blood is mixed with lymph. The embryos may leave the urinary organs by way of the urine.

The spreading of the embryos is effected, as Manson thinks, through the agency of mosquitos, which take them up in the act of sucking blood. The embryos attain a still higher stage of development inside the mosquitos, after which they make their way into water, and then once more into the human system. Probably their entrance into the latter is effected through the intestine. The correctness of Manson's views is, however, questioned by Leuckart.

The *Filaria sanguinis* occurs, as far as is known, only in the tropics—Brazil, Egypt, southern China, Calcutta, Bahia, and Guadeloupe.

Mackenzie estimates the number of filaria embryos present in the blood of a case of hæmatochyluria carefully observed by him, at from thirty-six to forty millions. The patient died of empyema, and the filariæ perished during this sickness.

Various species of filaria occur in the *domestic animals*, dwelling in various parts of the body. The *Filaria papillosa* is quite a common parasite of the horse, ass, and cattle, living in the serous cavities and possessing a length of from 5 to 18 cm. *Filaria hæmatica*, a worm from 13 to 25 cm. long, occupies the right side of the heart and the pulmonary artery of the dog, and there surrenders its embryos to the blood. It occurs especially in America, China, and India.

2. *Trematodes* (*Sucking-worms*).

§ 206. The **trematodes** are sucking-worms of tongue or leaf shape. They possess a clinging apparatus in the form of ventrally placed sucking-cups varying in number; sometimes they are also provided with hook- or clasp-like horny projections for the same purpose. The intestinal canal is without an anus, and is split like a fork through most of its extent. The development occurs either directly or after the method of alternate generation (through *germ-formation taking place inside of primary hosts*). The first hosts are pouches which chiefly occur in mol-

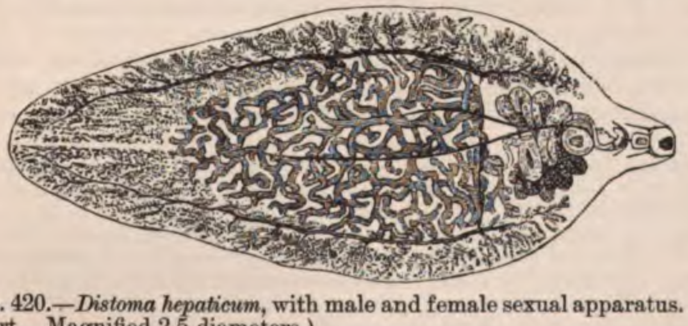


FIG. 420.—*Distoma hepaticum*, with male and female sexual apparatus. (After Leuckart. Magnified 2.5 diameters.)

lusks. The fully developed trematodes, with but few exceptions, are found in vertebrate animals. The progress to sexual maturity is furthered in the cases of alternate generation by an intermediate existence, usually passed in the lower animals, and ordinarily begun by an active migration. During this time the trematodes are fitted out with a rudder-like tail, by means of which they swim about in water as so-called *cercariæ*.

The **Distoma hepaticum**, or liver-leech, is a leaf-shaped sucking-worm 28 mm. long and 12 mm. wide (Fig. 420). The cephalic end projects like a beak, and bears a small sucking-cup, in which the mouth is located. Close behind this, on the ventral surface, is a second sucking-cup, and between the two lies the sexual orifice.

The uterus consists of a convoluted, bulb-shaped bag situated behind the posterior sucking-cup. On each side of the hinder part of the body lie the yolk-sacs, and between these the much-branched testicular canals. The forked intestinal canal also gives off numerous branches.

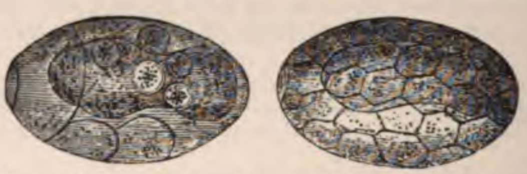


FIG. 421.—Eggs of *Distoma hepaticum*. (After Leuckart. Magnified 200 diameters.)

The eggs (Fig. 421) are oval, 0.13 mm. long and 0.08 mm. wide. A globular-shaped embryo develops in water, and with the help of a finely ciliated arrangement swims about and looks up a new host of the Mollusk family. According to Leuckart, the small limnæa of our marshes and meadows shelter the young of the liver-leech, taking for this purpose the form of a redia—that is to say, a germ-sac with an intestine, a birth-opening, and a water vascular system. In this redia there next appear germ granules, and from these develop *cercariæ*, which in form remind one of tadpoles. Lutz succeeded in developing liver-leeches by feeding guinea-pigs and goats on cercariæ and rediæ developed from limnæa, and he is of the opinion that the larvæ get into the liver through the portal vein. The sexually mature individual occupies the bile-ducts, and is found but seldom in the intestine or inferior vena cava. In man the *Distoma hepaticum* is rare, but is common in animals which chew the cud. The consequences of its invasion, especially when it is present in great numbers, are obstruction and ulcerating strictures of the bile-ducts, bile-stasis, dilatation and incrustation of the bile-ducts with bile-concretions, inflammation of the adjacent structures, and hyperplasia of the hepatic connective tissue with atrophy of the glandular structure.

Baelz has described three species of trematodes which occur in Japan, and which he calls *Distoma hepatis endemicum perniciosum*, *Distoma hepatis innocuum*, and *Distoma pulmonale*.* The last-mentioned species is from 8 to 10 mm. long, dwells in the lungs, and causes hæmoptysis. The *Distoma hepatis endemicum* is the size of a pea, and occupies the bile-passages, causing liver hypertrophies and diarrhœa. According to Winogradoff, there occurs not infrequently in Siberia a special kind of liver-leech, the *Distoma Sibiricum*, which, according to Brown, is possibly identical with the liver-leech of the cat (*Distoma felineum*).

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* Cf. Manson, *Lancet*, 1883.

§ 207. The **Distoma lanceolatum** is only 8 or 9 mm. long and from 2 to 2.5 mm. wide, is lancet-shaped, and the head section is not specially marked off from the body (Fig. 422).

The skin of the body is smooth. Two irregularly shaped testicles lie close behind the ventral cup, in front of the ovary and uterus, the coils of which shine through the transparent body. The anterior coils, which contain ripe eggs, are black, the rest being a rusty red. The yellowish-white yolk-sacs lie in the middle of the lateral margin.

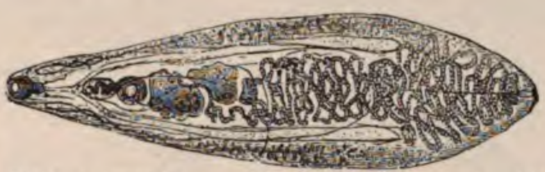

FIG. 422.—*Distoma lanceolatum* with its inner organs. (After Leuckart. Magnified 10 diameters.)

The eggs (Fig. 423) are 0.04 mm. long, and while still in the uterus contain an embryo, which does not escape, however, until several weeks after the eggs are cast off. Its metamorphoses are unknown.

The *Distoma lanceolatum* likewise occupies the biliary passages, but is very rare in man. It occurs more frequently in sheep and cattle. It is present only in small numbers, and therefore occasions no important changes; when great numbers do occur, inflammation and hypertrophy of the hepatic connective tissue may ensue.

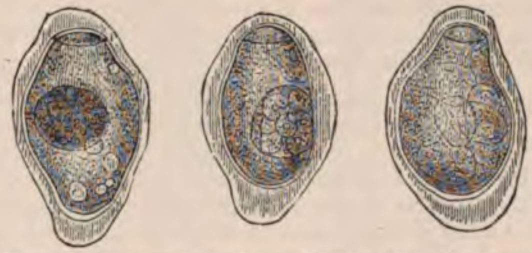

FIG. 423.—Eggs of *Distoma lanceolatum* shortly after the formation of a shell. (After Leuckart. Magnified 400 diameters.)

§ 208. In the **Distoma hæmatobium** (Fig. 424) the sexes are separate. The mouth and ventral cup lie only a short distance apart on the anterior extremity of the new-born individual. The sexual opening lies in both sexes close behind the ventral sucking-cup. The male is from 12 to 14 mm. long. Its body is smooth, but in its posterior portion is rolled up into a tube (Fig. 424) which serves for the reception of the female (canalis gynæcophorus).

The female is from 16 to 19 mm. long, and almost cylindrical. The eggs are an elongated oval (Fig. 425) measuring 0.12 mm. in length, and possess a terminal or lateral spine. According to Sonsino's observations, no alternate generation occurs in the development of the *Distoma hæma-*

tobium. The part of intermediate host is taken by small crustacea, into which the ciliated embryo, swimming around in water, bores its way to become encapsulated in the former's tissues. In all probability, then, infection occurs by drinking water infected with the larvæ.

The worms are found in the trunk and branches of the portal vein, the splenic vein, the mesenteric veins, and also in the rectal and vesical blood-vessels. They get their nourishment from the blood, and occur in men and apes. Their eggs pass through the mucosa and submucosa of the ureters, bladder, and rectum, and at times the liver, lungs, kidneys, and prostate as well. They give rise to inflammation of the bladder and ureters, with the formation of papillary and polypoid growths, ulcerations, incrustations, and concretions. While still within the urinary passages, cylindrical embryos provided with fine ciliæ may develop.

Fig. 424.

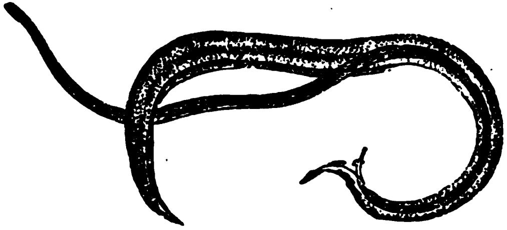

Fig. 425.

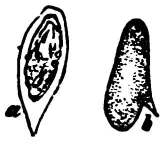

FIG. 424.—*Distoma hæmatobium.* (After Leuckart.) Male and female, the latter in the canalis gynæcophorus of the former. (Magnified 10 diameters.)

FIG. 425.—Eggs of *Distoma hæmatobium.* (After Leuckart.) *a*, Egg with terminal spine; *b*, Egg with lateral spine. (Magnified 150 diameters.)

The parasite occurs throughout the entire eastern coast of Africa, and also in Zanzibar, Tunis, Lake Nyassa, in Beyroot, and in Sicily. It is most common in Egypt, where 25 per cent. or thereabout of the native population suffer from this disease.

3. *Cestodes* (*Tapeworms*).

§ 209. The **tapeworms** are *flat worms devoid of mouth or intestine,* which increase after the method of alternate generation, through the germination of a pear-shaped primary host (head or scolex), and remain united to the latter for a considerable time as a (usually) long, band-shaped colony. The single members of this colony, the sexually active individuals, or **proglottides,** increase in size the more widely they become separated from their place of origin by the formation of new members, but outside of this are devoid of any outward peculiarity. The pear-shaped primary **host,** on the other hand, known as the *scolex* or **head,** is provided with from two to four suckers, and usually also with curved, claw-like hooks. With the help of these adhering organs the tapeworms fasten themselves to the intestinal wall of their intermediate host, which invariably seems to be one of the vertebrate animals. The scoleces develop out of a round embryo with from four to six hooks, and are found as so-called "measles" in the most diverse organs, chiefly the parenchymatous ones; later, they move out of these organs by a passive migration into the intestine of their future host.

The *tapeworms which occur as parasites in man* belong to different families—the *Tæniæ* and the *Bothriocephali*. The former live in man either as "measles" or as tapeworms. The latter occur in human beings as tapeworms only.

§ 210. The **Tænia solium** in its fully developed condition possesses usually a length of from 2 to 3 metres. Its *head* (Fig. 426) is as large as a small pinhead, and is spherical in shape; it has quite prominent sucking-cups. The crown of its head is not infrequently pigmented, and is the bearer of a fairly large rostellum with some twenty-six coarse, closely aggregated hooks, with short rootlets (Fig. 426). Following the head comes a filiform *neck* almost an inch long. A certain distance from the head there commences a division into segments. The first *segments* are very short, but their length increases from before backward (Fig. 427). They become first square and finally longer than they are wide. About 130 cm. behind the head the mature segments begin, though the sexual organs were fully developed in the earlier segments. The mature segments (Fig. 428) are, when stretched out, 9 or 10 mm. long and 6 or 7 mm. wide, and have their corners rounded off. The sexual orifice is situated laterally in the posterior half of the body. The uterus possesses from seven to ten lateral branches, which are separated from one another by a considerable distance, and end in a variable number of boughs branched like a tree. The uterus is filled with eggs.

The parenchyma of the body of mature as well as of immature *proglottides* (or tapeworm segments) (Fig. 429) is divided into two chief layers,

Fig. 426.

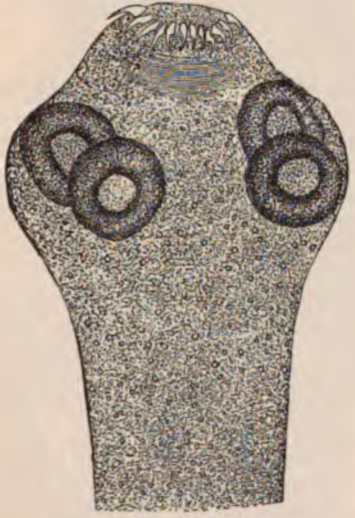

Fig. 427.

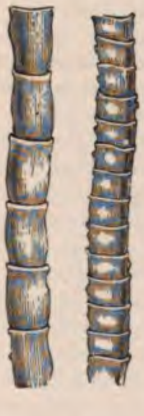

Fig. 428.

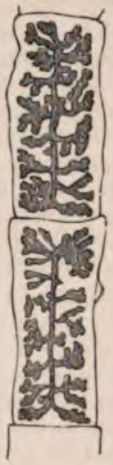

FIG. 426.—Head of *Tænia solium* with protruding rostellum. (Preparation stained with carmine and mounted in Canada balsam. Magnified 50 diameters.)

FIG. 427.—Half-developed and fully matured segments. (Natural size. After Leuckart.)

FIG. 428.—Two proglottides with uterus. (Magnified 2 diameters. After Leuckart.)

of which the central is known as the middle layer, the peripheral as the cortical layer. The middle layer includes the sexual organs (Fig. 429, *c, d, e, f, g, h, i, k, l, m, n*), and also the water vascular system (*a*), an excretory apparatus which traverses the whole tapeworm from head to last segment in the form of two canals located in the lateral border of the middle layer. The canals are connected with each other at the posterior end of each segment (a_1) and also send subdividing branches to the parenchyma of the body.

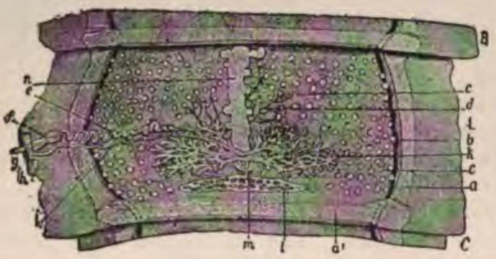

FIG. 429.—Segment of *Tænia solium* with fully developed sexual apparatus. (After Sommer.) A, Surface view of segment; B, Border of adjacent anterior segment; C, That of adjacent posterior segment. *a*, Longitudinal excretory trunk; a^1, Transverse anastomosis; *b*, Longitudinal plasma-vessel; *c*, Testicular vesicles; *d*, Seminal ducts; *e*, Vas deferens; *f*, Cirrus-bag with cirrus (or penis); *g*, Porus genitalis; *h*, Border papilla; *i*, Vagina; *k*, Ovary; *l*, Albumin gland; *m*, Shell-gland, and oviduct in front of same; *n*, Uterus. (Magnified 30 diameters.)

The *sexual apparatus* consists of male and female sexual organs lying close together (Fig. 429). A number of clear, small vesicles serve as testicles (*c*), lying chiefly in the anterior part of the middle layer. The vas deferens (*e*), which is connected with the testicles by the seminal ducts (*d*), opens into an umbilicated papilla located on the lateral border (*h*). The coiled end (*f, g*) lies in a muscular bag and may be protruded through the sexual orifice (*cirrus*). The female sexual orifice is located just back of the male orifice in the same sexual cloacus. The vagina (*i*) leads thence to the posterior border of the segment. Before reaching the latter it widens into the seminal vesicle, and behind this into the fructifying canal and the so-called "globular body." The germ-preparing organs, which are to be sought in the immature segments, consist of a double ovary (*k*) and a single albuminous gland (*l*); these are sac-like or tubular organs which lie in the posterior part of the segments and are connected with the globular body. The latter is joined to the anteriorly located uterus (*n*), which at the time of sexual maturity forms a straight canal. When the eggs enter the uterus from the globular body, in which they attain their first stage of development, the above-mentioned lateral branches sprout forth and become filled with eggs. While this is going on the remaining sexual organs disappear.

The *cortical layer of the proglottides* is essentially muscular in character, but in addition contains a larger or smaller collection of so-called calcareous bodies, which are not entirely wanting in the middle layer as well. The muscular supply consists of smooth fibres, which form special groups on the suckers of the head. The surface of the tapeworm is covered with a clear cuticle, which forms the hooks on the head.

The *eggs in the ovary* are thin-skinned, pale and yellow, almost globular cells. In the uterus they change into yellowish balls with a thicker, more or less opaque shell, which is covered with closely placed spicules

(Fig. 430, *a*). This shell is frequently surrounded by a second envelope, an albuminous layer (*b*) limited by a membrane, and in it are embedded nuclei (primitive yolk-skin, or vitelline membrane). The diameter of the eggs, not including the vitelline membrane, amounts to 0.03 mm.

Fig. 430.

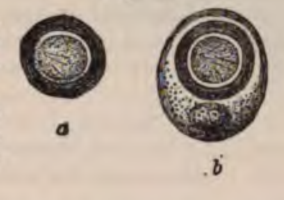

Fig. 431.

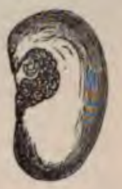

FIG. 430.—Eggs of *Tænia solium*. *b*, With vitelline membrane; *a*, Without latter. (After Leuckart. Magnified 300 diameters.)

FIG. 431.—*Cysticercus cellulosæ* with fully developed head *in situ*. (After Leuckart. Magnified 4 diameters.)

The thick-shelled balls are no longer undeveloped eggs, but contain an *embryo* with six hooklets. There takes place, then, while it is still in the uterus, a development of the embryo, and the fully developed segments are here impregnated.

The *further development of the embryos*, which are now inclosed in a brownish shell, does not take place in the same host which shelters the tapeworm, but in another. If the embryos reach the stomach of a pig the egg-shell becomes dissolved, and the embryos, thus liberated, bore their way into the wall of the stomach or intestine. Thence they proceed, either by way of the blood or by means of active migration, through the tissues into this organ or that. Having reached a resting-place the embryo undergoes various metamorphoses, and changes inside of two or three months into a *cyst* filled with serum (Fig. 431), from whose wall there shoots forth like a bud, toward the interior, a *scolex;* from this a new tapeworm head develops, as does also a sac enveloping the same (*receptaculum scolecis*).

The cyst provided with a tapeworm head is known as a "**measle**" or **Cysticercus cellulosæ.** The scoleces, when fully developed, possess a circle of hooks, suckers, a water vascular system, and numerous calcareous bodies in their body parenchyma. If they get into a human stomach the cyst dis-

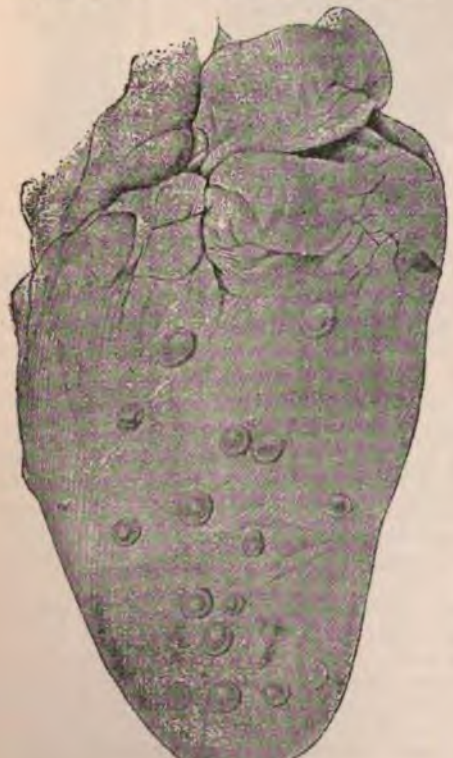

FIG. 432.—Cysticerci of the *Tænia solium* in the epicardium and muscular tissue of the heart of a pig.

solves, and there develops, through formation of segments from this primary host (*Amme*), a new chain of proglottides, a new *Tænia solium*.

The *Tænia solium* occupies the small intestine in man, and is acquired by the consumption of uncooked pork, since the "measles" belonging to this parasite occur almost solely in human beings and swine. Generally there is only a single parasite present in the intestine, though the simultaneous occurrence of several is not rare. Occasionally as many as thirty or forty are observed in one individual. They occasion irritation of the intestinal mucous membrane, colic, and reflex disturbances in the central nervous system.

The "measles" in the tissues of the swine are sometimes single, sometimes numerous (Fig. 432), and it can happen that single organs—as, for example, a muscle or the heart (Fig. 432)—may be thickly sprinkled with them.

In man the cysticerci occur in the most varied tissues—the muscles, brain, eyes, skin, etc. In the brain membranes and the brain itself the "measles" may appear in the form of collections of cysts bunched like mulberries or grapes, and called *Cysticercus racemosus* (Zenker). The cysts are mostly sterile, though some of them may contain a scolex. Their importance depends upon their location, but is generally slight, and even their presence in the brain does not always cause trouble. Locally their presence excites a slight inflammation, which leads to a thickening of the connective tissue

Fig. 433.

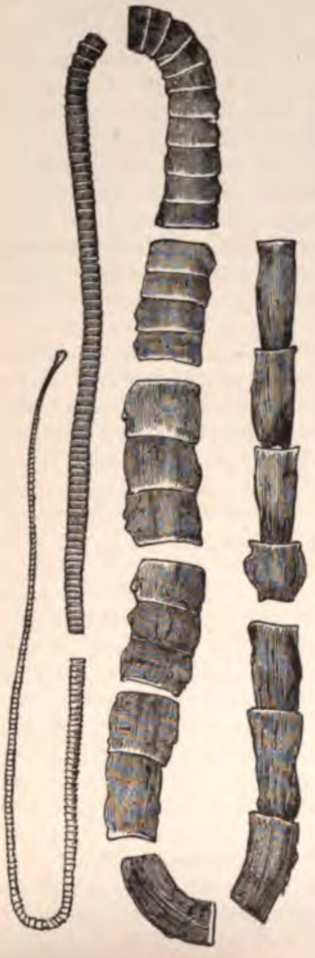

Fig. 434.

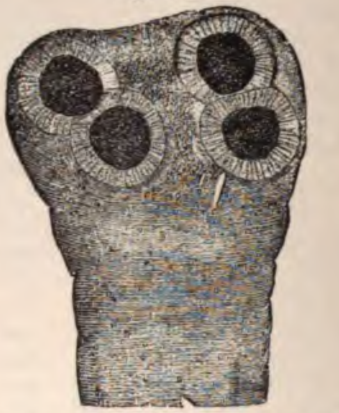

Fig. 435.

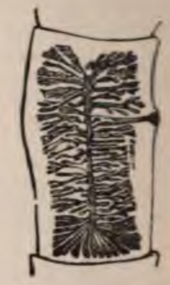

FIG. 433.—Sections from a *Tænia saginata*. (Natural size. After Leuckart.)

FIG. 434.—Head of a *Tænia saginata* drawn together. Black pigmentation in and between the suckers. (Unstained glycerin preparation. Magnified 30 diameters.)

FIG. 435.—Segment of *Tænia saginata*. (Magnified 1½ diameters. After Leuckart.)

in the immediate vicinity of the cyst. The latter retains its vitality for years. After the death of the scolex the cyst shrivels up, and within it there accumulates a chalk-like mass. In this mass the hooks remain a long time. Infection with the "measles" follows the presence of eggs or proglottides in the human stomach.

§ 211. The **Tænia mediocanellata** (or **saginata**) surpasses the *Tænia solium* not only in length (as much as from 4 to 7 metres and even longer), but also in breadth and thickness, as well as in the size of the proglottides (Fig. 433).

The *head* is devoid of rostellum and a circle of hooks (Fig. 434), but is provided with a flat crown and four large and powerful suckers, which are generally surrounded by a black fringe of pigment.

The *eggs* are similar to those of the *Tænia solium*. The fully developed, pregnant *uterus* (Fig. 435) has a great number of lateral branches which run close together and, instead of branching like a tree, divide only dichotomously. The sexual orifice lies posterior to the centre of the lateral border. The eggs are for the most part already discharged from those segments which become spontaneously separated from the rest.

The "*measles*" are found in the cow chiefly in the muscles and heart, more rarely in other organs, and are somewhat smaller than in swine.

The *development* follows a course similar to that of the *Tænia solium*. Irregularities of formation are very common in the tapeworm.

Human beings acquire tapeworms by the consumption of raw beef. This worm is more wide-spread than the *Tænia solium*.

The *Tænia cucumerina* (or *elliptica*) is from 15 to 20 cm. long, and possesses a head with a rostellum and a circle of hooks. It occurs very frequently in dogs and cats, but more seldom in man. Its cysticercoid infests the louse and flea of the dog, and more rarely the flea of human beings (Grassi [*]).

Tænia nana, a small tapeworm from 8 to 15 mm. long, has a head with four suckers and a circle of hooks. It has been observed in Egypt and Italy. B. Grassi [†] was able to obtain several thousand specimens from two Sicilians who had suffered from severe nervous disturbances. According to his investigations,[‡] the tænia passes its whole period of development, from the embryonal stage onward, in the interior of one host. Visconti found,[§] in an autopsy on a young man from northern Italy, *Tænia nana* in great numbers in the lower part of the ileum. According to Grassi, the *Tænia leptocephala*, which is common in mice, occurs also in man.

§ 212. The **Tænia echinococcus** lives in the intestinal canal of the dog. It is 4 mm. long, and possesses only four segments, of which the most posterior surpasses in length all the rest put together (Fig. 436).

The hooklets have coarse root processes and are implanted on a rostellum which bulges out considerably. The number of hooklets amounts to some thirty or forty.

Only the *cyst-worm* occurs in man. It follows the introduction of tænia eggs into the intestinal canal.

If the embryo chances to wander from the intestinal canal into some organ, it changes into a *cyst* which is incapable of active motion. It consists of an external elastic *cuticle divided into layers*, and a parenchymatous layer lying internal to this, consisting of granular matter and cells, and containing muscle-bundles and a circulatory system. When the cyst has reached the size of a walnut approximately (sometimes earlier), there are formed from the parenchymatous layer small *brood-capsules*, the delicate wall of which likewise consists of two layers, an inner cuticular layer and an outer parenchymatous layer. Upon these brood-capsules the small *heads* or *scoleces* (Fig. 437) develop in manifold numbers. They grow (according to Leuckart) out of hollow sacs which bulge out from the external wall of the brood-capsules (Fig. 437, on the left).

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[*] "Beiträge zur Kenntniss des Entwickelungscyclus von fünf Parasiten des Hundes," *Centralbl. f. Bakt.*, iv., 1888.

[†] *Centralbl. f. Bakt.*, i., 1887.

[‡] *Centralbl. f. Bakt.*, ii., 1887.

[§] *Rendiconti R. Instituto Lombardo*, xviii., 1886.

As soon as the heads on the outer surface of the brood-capsules have finished their metamorphosis into tapeworm heads (earlier at times), they project into the cavity of the capsules (Fig. 437). What was formerly the inner side of the young heads, the part provided with a cuticular covering, now becomes the exterior, while the cell-walls of the head, now brought into immediate contact, coalesce. The head is at this time about 0.3 mm. long, and possesses a rostellum with coarse hooklets, four suckers, a water vascular system, and numerous chalk-like bodies in its parenchyma. Frequently the anterior part of the body is telescoped into the posterior part (Fig. 437).

Fig. 436.

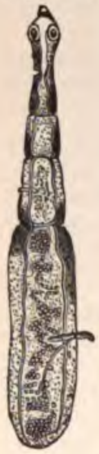

Fig. 437.

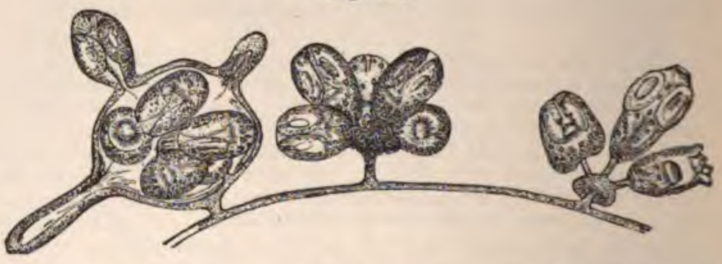

FIG. 436.—Full-grown *Tænia echinococcus*. (After Leuckart. Magnified 12 diameters.)

FIG. 437.—Brood-capsules, showing connection with the parenchymatous layer; some closed up and ruptured in preparing. (After Leuckart.)

In many cases the **echinococcus cyst remains single.** The only possible variation consists in an enlargement to the size of an orange or fist, through the development of new brood-capsules and heads. The surrounding tissue forms a connective-tissue capsule, in which the cuticular cyst lies inclosed. The cavity of the cyst is filled with a clear fluid, which does not precipitate on boiling or on the addition of acid. The brood-capsules are always fastened to the inner surface, unless mechanically dislodged, and are visible as small white points through the translucent cyst-parenchyma. Occasionally the cyst remains sterile.

In some cases **daughter-cysts** develop. Their development proceeds independently of the real parenchymatous layer in the depth of the cuticle. Between two lamellæ of the cuticle there is formed a collection of granules, which become surrounded by a new cuticle and in this way become the centre of a fresh set of layers. As the number of layers increases the cavity grows larger and its contents become clear. When the daughter-cysts grow they bulge out the wall of the parent-cyst like a hernial sac, until it finally gives way and liberates its contents. If these travel outward beside the parent-cyst they derive from the parenchyma in which they lie an external connective-tissue capsule, and then proceed to generate brood-capsules in the same way as do the primary cysts which grow from six-hooked embryos.

An echinococcus with an *exogenous proliferation* is called **Echinococcus granulosus** (*Scoleciypariens* of Küchenmeister), or sometimes **Echinococcus veterinorum,** because it occurs commonly in the domestic animals.

A second, compound form of the echinococcus is the **Echinococcus hydatidosus.** It is characterized by the presence of *inner daughter-cysts.* According to statements made by Naunyn and confirmed by Leuckart, the scoleces and brood-capsules may undergo a cystic metamorphosis and in this way become daughter-cysts. Leuckart opposes Naunyn's statement that these endogenous daughter-cysts migrate outward and thus generate the *Echinococcus granulosus.* The daughter-cysts occasionally, in a later stage of their existence, give origin to a third generation of cysts. All cysts occurring in the forms of echinococci thus far considered may attain a very considerable size.

The third form of echinococcus, the **Echinococcus multilocularis,** never develops any but small cysts which vary in size from that of a millet-seed to that of a pea, but these cysts are invariably present in larger numbers. This echinococcus presents itself as a firm tumor, located usually in the liver, very rarely in other organs, and possessing an

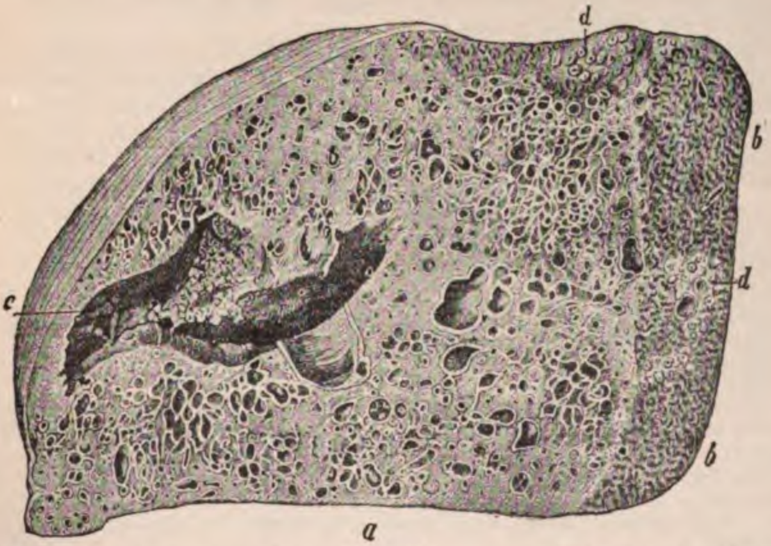

FIG. 438.—Transverse section of an *Echinococcus multilocularis.* *a,* Alveolar structure of the echinococcus tissue; *b,* Liver-tissue; *c,* Cavity produced by softening; *d,* Fresh nodules. (Natural size.)

alveolar structure (Fig. 438)—that is, a thick, compact connective-tissue mass inclosing numerous cavities. Its contents are gelatinous and translucent, or else consist of a fluid and a gelatinous mass. The shape of the cavities is somewhat globular at times, at others irregular. Usually through softening and destruction of the parenchyma ulcerous cavities (*c*) are formed here and there. In other places the cysts are shriveled up and calcified, or the tissues are infiltrated with bile. Where the development of the colonies has progressed further there appear in the tissues yellow nodules (*d*) in which a dark centre soon forms, later becoming liquid. The exquisite alveolar structure has given rise to the theory that echinococcus is an alveolar tumor with colloid contents. Virchow was the first to recognize the real nature of the process and to demonstrate that the so-called colloid masses are echinococcus cysts. The contents of the smallest cysts are granular masses; in larger ones the contents have become liquefied. The granular coating of the cuticle only rarely contains scoleces, the cysts being for the most part sterile.

Whether the multilocular echinococcus is a modification of the exogenous proliferating echinococcus or a separate species is as yet undetermined. Mangold and Müller consider it a distinct species.

The *infection of human beings* follows the chance ingestion of eggs of the tænia which occurs in dogs. The liver is the most frequent site of the cysts, but the echinococcus occasionally occurs in the most diverse organs—e.g., the lungs, spleen, intestine, bones, or heart. Apart from the disturbance of the tissues and the local inflammation which it excites (the latter cause leading in some organs to the formation of a connective-tissue capsule), it frequently has no harmful effect whatever on the patient. It often dies on attaining a certain size (from the dimensions of a walnut to those of an apple), the liquid becomes absorbed, the cyst shrivels up, and there remains within only a fatty, caseous detritus, which often calcifies to a mortar-like mass. The hooks may be found in this mass for a very long time.

In other cases the echinococcus enlarges, especially if endogenous or exogenous daughter-cysts develop. Under these circumstances it may become dangerous on account of its size. Occasionally, especially following traumata or rupture of the cysts into one of the body-cavities, severe inflammations ensue. Rupture into the blood circulatory system also occurs, and may lead to a transplantation of the cysts and to a plugging of the vessels. In more favorable cases the rupture points outwardly or into the intestine.

The echinococcus is very wide-spread, though not very common. It occurs most frequently in Iceland, where the inhabitants live in close contact with dogs. It is a striking fact that the multilocular form is chiefly observed in Switzerland and in southern Germany.

Tæniæ, exclusive of the kinds shared in common with man, occur very frequently in the *domestic animals*, and not only in the Carnivora and in birds, but in the Herbivora.

The *Tænia marginata* of the dog is a tapeworm from 1 to 5 metres long, provided with a double circlet of hooks, living as a cyst-worm in and beneath the serous membranes of sheep, cattle, goats, and swine, and forming cysts of various sizes.

The *Tænia serrata*, a tænia of the dog, some 50 to 100 cm. long, armed with hooks, is the developed state of certain cysticercæ occurring in rabbits and hares.

The *Tænia cœnurus*, a tapeworm of the dog, some 40 to 100 cm. in length and provided with hooks, passes its cystic stage most frequently in sheep. Here it seeks out the central nervous system and forms cysts which vary in size from that of a millet-seed to that of a hen's egg, and which produce great numbers of scoleces. Their presence in the brain causes the so-called "staggers."

§ 213. The **Bothriocephalus latus**, or **pithead**, is the most formidable tapeworm of man, measuring, as a rule, from 5 to 8 metres in length, and being made up of from three to four thousand short but broad segments (Fig. 439); these are broadest in the middle region and get narrower at the end. The length of the largest segments amounts to 3.5 mm.; the width from 10 to 12 mm.

Fig. 439.

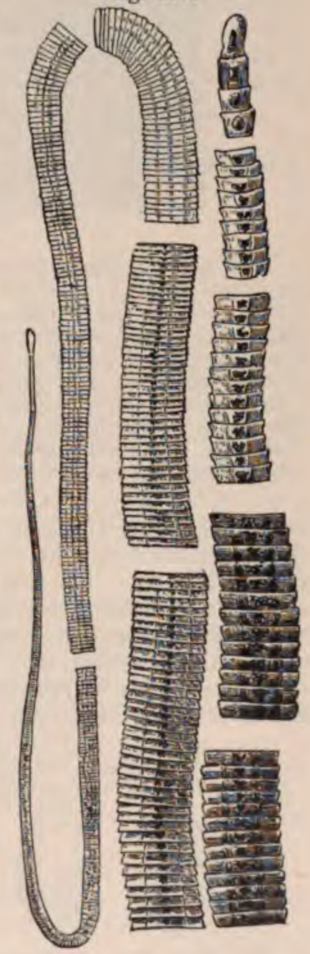

Fig. 440.

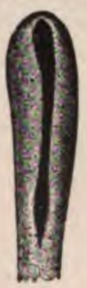

FIG. 439.—*Bothriocephalus latus.* (After Leuckart. Natural size.)

FIG. 440.—Head of *Bothriocephalus latus* of Bremser. (Magnified. After Heller.)

The *head* (Fig. 440) has an elongated oval or club shape, is 2.5 mm. long and 1 mm. wide, and is somewhat flattened down. It possesses on each lateral border a slit-like depression, and is mounted on a filiform neck.

The *body* is thin and flat like a ribbon, except the central parts of the segments, which project somewhat outward. At this spot the uterus is found, in the shape of a simple canal, which forms a number of coils (Fig. 441, *m*). When the eggs collect here in great numbers the lateral coils of the uterus arrange themselves in knots, so that a remarkable rosette-like appearance is produced. The sexual orifices lie in the median line of the ventral surface, near the anterior border of the segment, the female orifice (*o*) being close behind the male (*f*).

The ovary (*g*) is a double organ which lies in the middle layer. The yolk-chambers (*h*), on the other hand, are located in the cortical layer. Back of the collecting-tube (*i*) of the yolk-chambers lies the shell-gland (*k*). The testicles consist of clear vesicles (*b*) lying in the lateral part of the middle layer and connected by means of fine canaliculi (*c*) with the vas deferens (*d*), which terminates in the cirrus-sac (*e*, *f*).

The *eggs* (Fig. 442) are oval, and have a length of 0.07 mm. and a breadth of 0.045 mm. They are surrounded by a thin brown shell, the anterior pole of which is formed by a sharply limited cap-like cover.

The *Bothriocephalus latus* occurs especially in Switzerland, north-

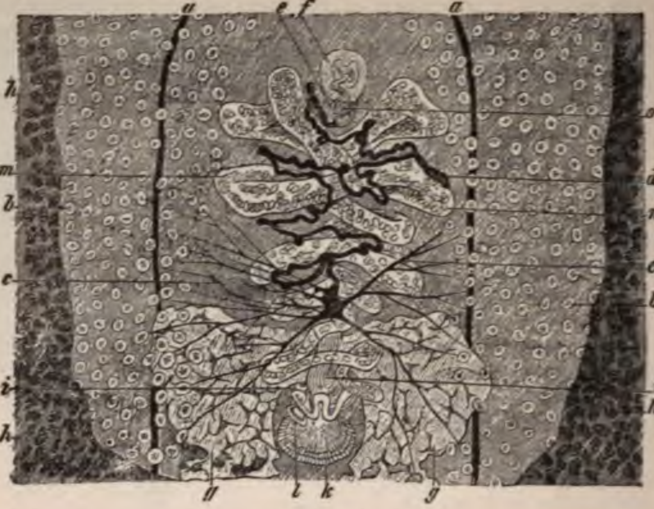

FIG. 441.—Median portion of a proglottis of the *Bothriocephalus latus*, showing dorsal surface. The cortical layer of the segment has been removed, except a border on each side, and the middle layer thus exposed. (After Sommer.) *a*, Lateral vessels; *b*, Testicular vesicles; *c*, Testicular canaliculi; *d*, Vas deferens; *e*, Posterior, *f*, anterior hollow muscle arrangement (cirrus-sac of vas deferens); *g*, Ovary; *h*, Yolk-chambers, situated in cortical layer; *i*, Collecting-tube of yolk-mass, branches of which lead ventrally to the yolk-chambers; *k*, Shell-gland; *l*, Beginning of uterus; *m*, Knot of uterus filled with eggs, with orifice opening on the anterior surface; *n*, Vagina; *o*, Vaginal orifice. (Magnified 35 diameters.)

eastern Europe, Holland, and Japan, and lives, like the Tænia, in the small intestine of man. According to Bollinger, it is also quite common in Munich. The first development of the eggs takes place in water. Months afterward there develops an embryo (*Oncosphæra*), armed with six hooklets (Fig. 443) and covered with minute ciliæ. This develops in an intermediate host (as yet unknown) to a "measle" (*Plerocercoid*), which, according to the investigations of Braun in the Russian Baltic Sea provinces, seeks out as second mediate host the pike or tadpole, and either in

Fig. 442.

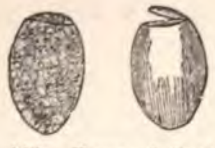

FIG. 442.—Eggs of *Bothriocephalus latus*, the one to the right having been emptied of its yolk-contents. (After Leuckart.)

Fig. 443.

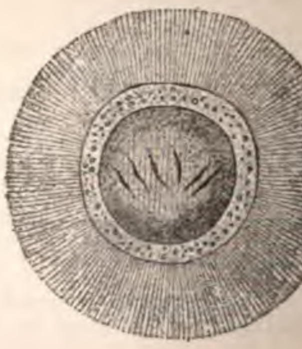

FIG. 443.—Free embryo of *Bothriocephalus latus*, with ciliated envelope. (After Leuckart.)

the muscles or in the intestines of these fish develops to a sexless tapeworm. According to Grassi and Parona, the "measle" of the *Bothriocephalus latus* occurs in Italy both in the pike and in the river-perch; in Japan it is found most often (Ijima, Leuckart) in the *Oncorhynchus Perryi*. Zschokke found it in the following fishes of the Lake of Geneva: *Lota vulgaris*, *Perca fluviatilis*, *Salmo umbla*, *Esox lucius*, *Trutta vulgaris*, and *Trutta lacustris*. It is most frequent in the tadpole (*Lota vulgaris*) and the perch (*Perca fluviatilis*). If it reaches the intestinal canal of man by ingestion of the afore-mentioned fishes it again attains sexual maturity. According to Braun and Parona, the "measle" may also be brought to development in the dog and cat. The presence of bothriocephali in the intestine may give rise to a gradually progressing *anæmia*, which resembles pernicious anæmia. How the presence of the Bothriocephalus causes a diminution in the red blood-corpuscles and the percentage of hæmoglobin in the blood is unknown.

In Greenland there occurs in dogs and man another bothriocephalus, which grows only 1 metre long, and possesses a heart-shaped head. It is known as the *Bothriocephalus cordatus*.

III. Protozoa.

§ 214. Of the **Protozoa** occurring as parasites in man, but a small number were recognized up to a few years ago, and even the recognized forms were of but slight importance, since there could be ascribed to them no particular influence on the tissues. Following the investigations of the last few years, however, various species have become known which must be regarded as the cause of morbid processes, and it is quite possible that there exist still other protozoa besides those already described which can bring about pathological changes in the human body. Representatives of all four classes of the Protozoa have already been observed.

Of the **Rhizopoda** there occur in the intestine three amœbæ, known as the **Amœba coli vulgaris, Amœba coli mitis** (Roos, Quincke), and **Amœba dysenteriæ** (Kartulis, Osler, Councilman, Lafleur, Kruse, Pasquale). The *Amœba dysenteriæ* is certainly distinguishable from the other two forms, while the *Amœba coli vulgaris* and the *Amœba coli mitis* resemble each other very closely and may possibly be identical.

The *Amœba coli vulgaris* is a harmless intestinal parasite occurring (according to Roos, Kruse, and Pasquale) not infrequently in the bowel. Roos observed the *Amœba coli mitis* in a case of chronic enteritis, the patient having always lived in North Germany.

The *Amœba coli mitis* consists, according to Roos, in a protoplasmic cell-body 25 to 35 μ in diameter in its globular form, exhibiting slow motion and very frequently assimilating foreign bodies (Fig. 444, *a*)—for example, bacteria and crumbs of food. Besides the movable form there occur (according to Roos) also encysted globular forms, surrounded by a membrane with a

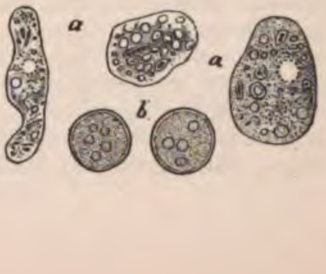

FIG. 444.—*Amœba coli mitis*. (After Roos.) *a*, Freely movable amœbæ; *b*, Encysted amœbæ. (Magnified 665 diameters.)

double outline, and inclosing clear round vesicles in their interior (Fig. 444, *b*). No pathogenic properties are disclosed if they are fed to animals (cats).

The *Amœba dysenteriæ* (identical with the *Amœba coli* described by Loesch) measures in diameter, according to Roos, from 15 to 25 μ, but according to Kruse and Pasquale, from 10 to 50 μ. On the cell-body are recognizable a homogeneous ectoplasm and a changeable granular entoplasm, the arrangement of which varies with the form of the amœba (Fig. 445, *a*). On staining, a nucleus in the interior becomes visible. The cells are capable of active motion, and assume thereby the most varied forms (*d*). Very frequently they contain foreign bodies in their interior, especially red blood-corpuscles or fragments of them (*b*), or else are perforated by clear vacuoles (*c*). Roos says they may also become encysted (*e*).

According to the investigations of Koch, Kartulis, Kruse, and Pasquale, they are invariably present in the dysentery prevailing in Egypt, and are usually also demonstrable in the fæces. They have also been observed in cases of dysentery in Russia (Loesch, Massiutin), in America (Osler, Councilman, Lafleur, Lutz, Dock), in Germany (Roos), and in Austria (Kovács). According to the investigations of Kartulis, Councilman, Lafleur, Kovács, Roos, Kruse, Pasquale, and others, there is probably no reason to doubt that they are of some significance in the origin of certain forms of dysentery. But even then it is a question whether they are able to bring about morbid changes of themselves or only when acting in conjunction with bacteria; the fact that when occurring in the tissues they are invariably accompanied by bacteria may be considered as confirmatory of the latter theory.

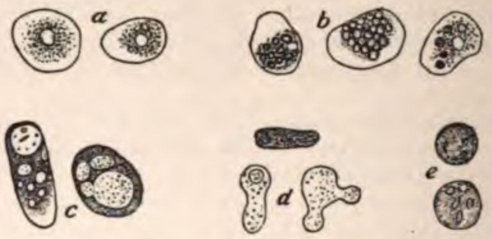

FIG. 445.—*Amœba dysenteriæ* or *Amœba coli felis*. (After Roos.) *a*, Amœbæ without any foreign contents; *b*, Amœbæ containing blood; *c*, Amœbæ with large vacuoles in their protoplasm; *d*, Young forms; *e*, Encysted forms. (Magnified 665 diameters.)

The **dysentery due to amœbæ** is characterized by the occurrence of a hæmorrhagic catarrh and the development of circumscribed ulcers with undermined borders. The amœbæ not only multiply in the intestinal mucous membrane, but, according to Councilman, Lafleur, Roos, Kruse, and Pasquale, penetrate in even greater numbers into the mucosa and submucosa, and develop here great colonies, in the neighborhood of which the tissues become necrotic, even without any considerable quantity of exudation having collected. Following the perforation of the submucous centres of disease through the mucosa, there ensue ulcers with undermined edges, which, gradually enlarging, may attain a very considerable size.

If *abscesses of the liver* arise in the course of amœbic dysentery they contain not only bacteria, but also amœbæ, and it is to be considered that the latter as well as the former are concerned in the disturbance of the liver-tissues.

The *Amœba dysenteriæ is also pathogenic in cats*, causing, after being fed to them or introduced into the rectum, a rapidly progressing and frequently fatal dysentery which resembles exactly the amœbic dysentery occurring in man; in them, also, the amœbæ penetrate into the mucosa and submucosa.

Of the class **Infusoria** there occur both the flagellate and the ciliated varieties. Of the latter the best known is the **Paramæcium** or **Balantidium coli** (Fig. 446). This is a large infusorium, thickly covered with ciliæ, occurring occasionally in the large intestine and the fæces. Of the flagellate Infusoria, the first to be mentioned is the **Cercomonas intestinalis** (Fig. 447), a pear-shaped creature with a spinous process at the pointed end and a flagella at the blunt end. It is found likewise in the intestine in catarrhal conditions, as in typhus and cholera cases. According to Bütschli and Perroncito, it is identical with the **Megastoma entericum** of Grassi and the *Megastoma intestinale* of Blanchard, and partially passes off in the fæces in an encysted condition (Perroncito), especially if there is no diarrhœa present. It also occurs in mice, rats, cats, dogs, sheep, and rabbits (Grassi), and fastens itself to the surface of the intestinal epithelia.

Kannenberg found cercomonas in the sputum in gangrene of the lung. There occurred in conjunction with the foregoing the **Monas lens**, a globular infusorium with a flagella. Streng communicates a similar observation.

Of the **Trichomonas**, an oval infusorium with several flagellæ and a comb-like, undulating fringe mounting its full length, there occurs one species in the vagina—the **Trichomonas vaginalis** (Fig. 448)—and one in the intestine—the **Trichomonas intestinalis** (Fig. 449).

Marchand found trichomonadidæ with four filiform flagellæ and an undulating fringe in the urine of a man. These are probably identical with the *Trichomonas vaginalis*, in which four filiform flagellæ also

Fig. 446.

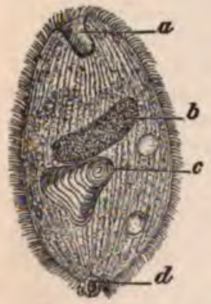

Fig. 447.

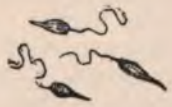

Fig. 448.

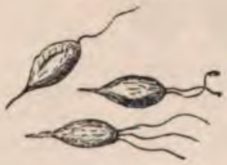

Fig. 449.

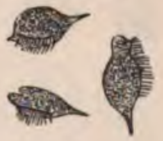

FIG. 446.—*Balantidium* (*Paramæcium*) *coli.* (After Claus.) *a*, Mouth; *b*, Nucleus; *c*, A granule of starch which has been ingested; *d*, A foreign body in the process of being expelled. (Highly magnified.)

FIG. 447.—*Cercomonas intestinalis.* (After Davaine.)

FIG. 448.—*Trichomonas vaginalis.* (After Kölliker.)

FIG. 449.—*Trichomonas intestinalis.* (After Zenker.)

occur. Miura also furnishes a similar observation. Grimm saw whip-infusoria in a liver-abscess and an abscess of the lung. Lindner found infusoria belonging to the ciliated class in the crusts of an itching eczema of the scalp.

§ 215. Of the **Sporozoa** or **Gregarinæ** which occur as parasites in man, the **Coccidia** must first be mentioned. According to Leuckart, in the young state they exist as non-capsulated occupants of epithelia. After their growth has ceased they become inclosed in a shell. In this condition they abandon their resting-place, and generally their host, and develop from their contents spores containing granular masses and remarkable rod-like embryonal forms. The spores are spherical or ovoid. The **Coccidium oviforme** (Fig. 451) is a parasite of the intestine and bile-ducts, occurring especially in rabbits. According to the observations of Podwyssozki, hens' eggs may also contain coccidia. In some cases they have been observed in man. Künstler and Pitres found coccidia in man in the exudation in a case of pleuritis, and Podwyssozki found them in the liver.

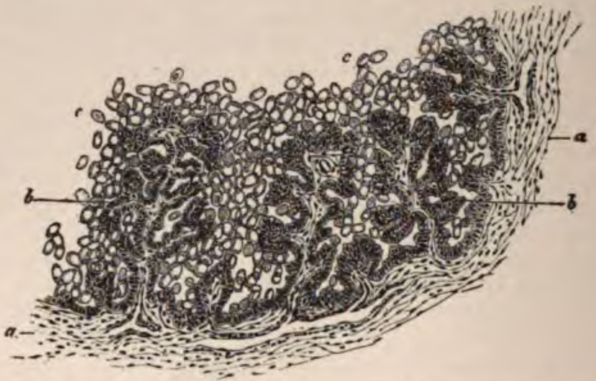

FIG. 450.—Section through the wall of a dilated bile-duct, filled with coccidia and the seat of papillary growths, occurring in a rabbit's liver studded with coccidia-nodules. *a*, Connective tissue; *b*, Branched papillary growths filled with epithelium; *c*, Coccidia. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 25 diameters.)

In the liver of rabbits the invasion of coccidia leads to the formation of white nodules, which may reach the size of a hazelnut, and are known as *coccidia-nodules*. The nodules contain a white or yellowish-white mass, and consist principally of dilated bile-passages, the interior of which is more or

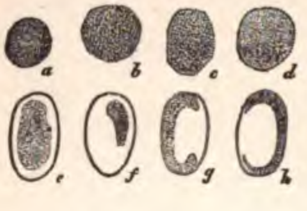

FIG. 451.—Coccidia from the bile-ducts of the rabbit's liver shown in Fig. 450, in various stages of their development. *a*, *b*, Small, coarsely granular early forms; *c*, *d*, Larger forms with darkly stained peripheral granules; *e*, *f*, *g*, *h*, Oval encapsulated forms, the granular protoplasm of which—partly coarse and partly fine—fills out only a part of the capsule. (Preparation hardened in Müller's fluid, stained with hæmatoxylin, and mounted in Canada balsam. Magnified 400 diameters.)

less richly furnished with papillary growths (Fig. 450), and the lumen of which contains immense numbers of coccidia.

The Coccidia exist in the bile-ducts partly in the form of a shell-less protoplasmic structure, partly in the form of encapsulated bodies. The smallest coccidia (presumably to be regarded as early forms) exhibit a coarsely granular protoplasmic formation (Fig. 451, *a*, *b*), in the interior of which now and then a nuclear appearance (*a*) is recognizable. The larger forms exhibit on their outer surface regularly arranged granules (*c*, *d*), which stain deeply with hæmatoxylin. The encapsulated forms occur as oval, double-contoured, clear-looking bodies (*e*, *f*, *g*, *h*), in the interior of which lies a variously shaped mass with a variable amount of granular matter, the latter never taking up but a portion of the space in the capsule. According to R. Pfeiffer, the granular coccidia which are not encapsulated may split up in the animal body into a great number of *sickle-shaped germs*, and in this manner increase in number. There appear at one pole, whose position is indicated by a round mass (the nucleus), radiating septa, which wedge their way through the plasma. Probably the sickle-shaped germs become transformed into small amœboid masses of protoplasm.

Provided the encysted coccidia reach the outer world, there may arise, under suitable conditions, inside of the protoplasm (which has drawn itself together like a ball) (Fig. 452, *b*) four *sporocysts* or *sporoblasts* (Fig. 452, *c*, *d*, *e*, *f*). Inside of these sporocysts develop formations which are primarily globular, later oval, and which later on produce two sickle-shaped germs apiece (*g*, *h*, *i*, *k*, *l*, *m*, *n*, *o*, *p*).

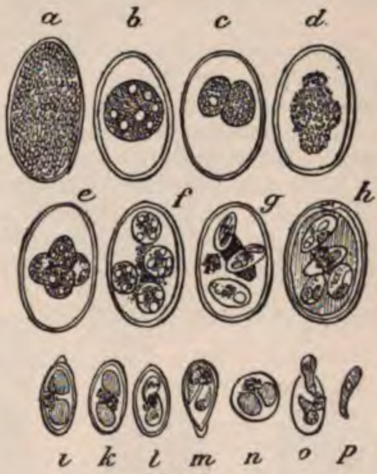

FIG. 452.—Development of spores in encysted coccidia. (After L. Pfeiffer.) *a*, Mature encapsulated parasite with evenly distributed protoplasm; *b*, Protoplasm collected together into a ball; *c*, *d*, *e*, *f*, Development of four sporocysts, a protoplasmic residue remaining; *g*, *h*, Developing, *i*, *k*, *l*, *m*, *n*, fully developed sickle-germs inside the sporocysts; *o*, Sickle-germ leaving sporocyst; *p*, Free sickle-germ. (Magnified 750 diameters.)

To the *Coccidia* probably belong also certain **parasites** which occur in the epidermis in man, and here produce peculiar growths known as **epithelioma contagiosum** (Fig. 453). In its fully developed condition the growth consists of a nodule the size of a small pea or larger, which projects above the surface of the skin, shows a small depression in the centre, and possesses a waxy lustre.

In the section there may be recognized an irregular epithelial growth (Fig. 453, *d*) with a central orifice opening outward (*g*)—that is to say, a formation which recalls a gland, and, indeed, is frequently considered as a hypertrophic sebaceous gland, but which is, however, only an independent new growth of epithelium brought about by the parasites.

The parasites develop inside the epithelial cells of the irregular growth

(Fig. 453, *e*), but are pushed toward the central orifice of the new growth by the epithelial cells behind (*f*), and here they lie in a meshwork of cast-off and horny epithelial cells.

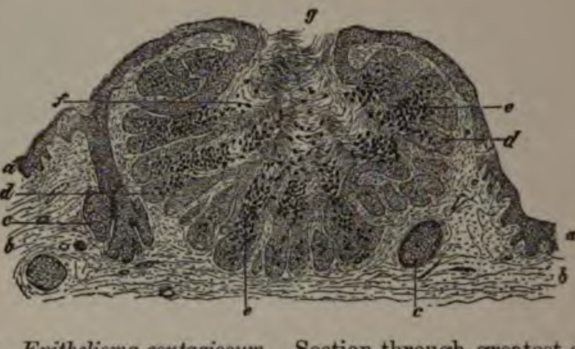

FIG. 453.—*Epithelioma contagiosum.* Section through greatest diameter. *a*, Epidermis; *b*, Connective tissue; *c*, Sebaceous gland; *d*, Gland-like epithelial growths; *e*, Parasites; *f*, Horny cells mingled with parasites; *g*, Duct filled with horny epithelium and parasites. (Preparation hardened in Müller's fluid, stained with hæmatoxylin and eosin, and mounted in Canada balsam. Magnified 15 diameters.)

Representing the earliest stage of development of the parasites, there arise in the epithelial cells small protoplasmic bodies (Fig. 454, *a*, *b*), the borders of which are only with difficulty to be distinguished from the cell-protoplasm; occasionally, however, they contain in their interior small distinct granules, and become through them more distinct. Later on their size increases, until finally they completely fill up the epithelial cells (*c*, *d*, *e*), so that the nucleus is pushed aside. At the same time the granules on the inside increase in number (*c*) and grow into larger bodies, so that the parasite finally becomes divided into a greater or less number of finely granular structures (*d*, *e*, *f*) lying in a finely granular network. During this time the cell-nucleus is destroyed.

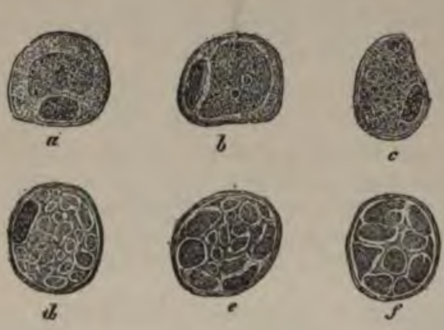

FIG. 454.—Parasites of *Epithelioma contagiosum* in various stages of development, lying inside epithelial cells. *a*, *b*, Epithelial cells inclosing a protoplasmic body inside of which lie single large granules; *c*, An epithelial cell almost completely filled with parasites; *d*, *e*, *f*, Parasites which completely fill the cell they occupy, and which have become divided into numerous separate bodies lying in a granular network; the cell-nucleus has been destroyed in *f*. (Mounted as in Fig. 453. Magnified about 500 diameters.)

The epithelial cells which inclose parasites early develop a distinct membrane, which grows more and more distinct and surrounds the parasites. Those parasites which have been expelled from the cells form oval bodies which appear to be inclosed in a capsule and present a homogeneous appearance. They stain deeply with hæmatoxylin.

The contagious epitheliomata may appear in great numbers in one and the same individual, and several persons living together may be either simultaneously or successively attacked. The spread of the disease may, then, be referred to contagion.

Our knowledge of the significance of the so-called "**sacs of Miescher**" is still scanty. They are sac-shaped structures (Fig. 455, A, B) occurring not infrequently in the muscles of swine, cattle, sheep (especially in the œsophagus), and in mice. They lie inside the muscle-cells (Fig. 455, B), and when slightly magnified look not unlike trichinæ. In the fully developed parasite the contents of the sac are differentiated into single segments defined by a membrane (Fig. 455), and these in turn inclose globular (A, C) or kidney- and sickle-shaped bodies (D, E). The parasite is classed among the *Sarcosporidia*. The separate segments are known as *sporocysts* or *sporoblasts*, since in their interior the kidney- or sickle-shaped *spores* arise (*Rainey's bodies*), and from these latter, under suitable conditions, new Miescher's sacs may develop (Pfeiffer). Ingestion of meat containing sarcosporidia is not dangerous for human beings.

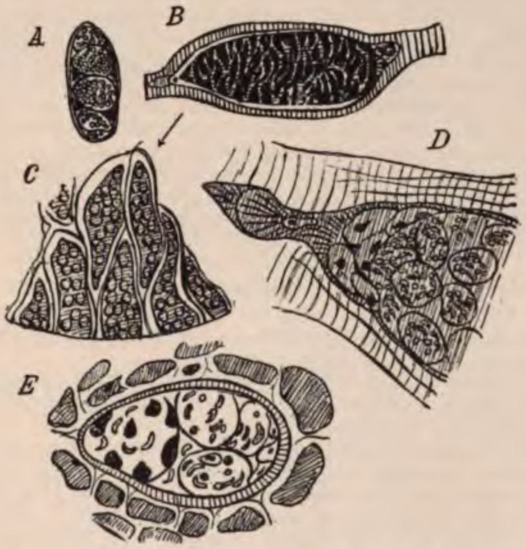

FIG. 455.—Miescher's sacs in various phases of development, taken from swine and sheep. (After L. Pfeiffer.)

A, Sarcospore with four sporocyst globules, taken from the cardiac muscle of a sheep. (Magnified 120 diameters.)

B, Sarcosporidia-sac in a striped muscle of the swine. (Magnified 120 diameters.)

C, Terminus of a sac with sporocysts, the latter containing round spore-cells. (Magnified 500 diameters.)

D, Terminus of a sac containing both undeveloped and mature sporocysts. At the left end, a pseudopod shaped like a cloak and covered with hairs. (Magnified 500 diameters.)

E, Transverse section through a sac with sporocysts, containing sickle-shaped spore-cells. (Magnified 500 diameters.)

The last few years have produced a very unusual number of reports of *parasites said to belong to the Sporozoa or Gregarinæ*, and numerous authors have considered that they were justified in ascribing various morbid processes, chiefly pathological epithelial formations, and of these more especially cancer, to the presence of gregarinæ. It may, however, be remarked that only a very small part of what have been described as parasites are really to be looked upon as such; so that, so far as man is concerned, the occurrence of parasitic gregarinæ is restricted to a few distinct diseases.

So far as *carcinoma* is concerned, notwithstanding the great number of works on the subject (so numerous that they can scarcely all be perused—e.g., Stroebe's collection), the proof is by no means forthcoming that protozoa, especially gregarinæ, are present inside the epithelial growths, or are to be considered as the cause of the latter. All the appearances described, even the sickle-shaped form and those provided with a sort of capsule, which have been seen in cancer-cells and considered convincing, permit of another explanation, and, in my opinion, are to be interpreted partly as changed nuclei, partly as altered protoplasm of the cancer-cells or as dissolution of the cells, and, finally, some may be explained as a product of cell-fusion, or of the assimilation of one cell by another.

The disease described by Darier as *psorospermose folliculaire végétante*, and referred by him to the presence of sporozoa, is very probably only a skin affection characterized by a pathological keratosis (keratosis follicularis of White), in which little horny plugs and pegs are developed one by one in the epithelium of the skin of some part of the body, the cutis exhibiting mild inflammatory symptoms. According to Buzzi, Miethke, Rieck, Krösing, Petersen, and others, the *corps ronds*, described by Darier as parasites, contain keratohyaline and eleidin—that is to say, substances which occur in horny cells, but not in gregarinæ.

Paget's disease is a process which spreads from the nipple, commencing with an inflammation resembling eczema and leading to superficial ulceration, said to finally end in a cancerous infiltration of the skin. It has been referred by Darier, Wickham, Malassez, and others to a parasite—a sporozoön which multiplies in the epithelial cells. It is, however, an eczema arising from other causes, and finally leading to cancer, or else a primary cancer accompanied by inflammatory changes, in which characteristic alterations occur in the epidermis—namely, swelling up of the protoplasm and nuclei, and development of vacuoles; there also develop some new growths, the characteristic views of which simulate parasites.

I consider the bodies found in molluscum as parasites (as already appears from the main text), though this opinion is opposed by various authors (Kromayer, Hansemann, Török, and others). The growths have totally different characteristics from those described in cancer.

Rosenberg reports the discovery of sarcosporidia in the muscle of the human heart. Kartulis made a similar discovery in an abscess of the liver and in the abdominal muscles of a Sudanese.

Pisenti, Silcock, Eve, Bland Sutton, and Jackson Clarke have pointed out the possibility that the cysts occurring in the urinary passages leading from the ureters, in *ureteritis cystica*, may be of parasitic origin. Lubarsch and Aschhoff have expressed themselves as opposed to this theory. From the later investigations of von Kahlden, it has nevertheless been made very probable that the ureteritis cystica is really caused by sporozoa.

According to Hess and Guillebeau, coccidia may occasion diarrhœal diseases of the intestine in young cattle.

Guarneri[*] declares that protozoa belonging to the Coccidia are the cause of smallpox.

§ 216. Through the investigations of Laveran, Marchiafava, Celli, Golgi, and others, it may be considered proved that the *cause of malaria* is a parasite belonging to the Protistæ, which has been named by Marchiafava and Celli the **Plasmodium malariæ**, and which at the present time is commonly known by this name. The parasite exists in the blood of malaria patients in various forms, chiefly inclosed in cells; and, according to the observations of Golgi, Celli, Marchiafava, and others, a certain connection may be traced between the number and stage of development of the plasmodia and the attacks of fever. The parasites run through many stages of development in the interval between the separate attacks of fever, the stages (according to the authors mentioned) being different in the febris quartana, the febris tertiana, and the febris quotidiana; at the same time the parasites of the various forms of fever exhibit certain differences in their physiological characteristics.

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[*] "Ric. sulla patogen. ed etiol. dell' infezione vaccinica e variolosa," *Arch. per le Sc. Med.*, xvi., 1892.

The development and increase of the plasmodia take place in the interior of the red blood-corpuscles, where, first of all, small, colorless amœboid bodies appear (Fig. 456, *a*). In the *febris quartana* the further development is inaugurated by an enlargement of the small amœboid beginning forms (Fig. 456, *a*, *b*, *c*, *d*, *e*), so that the red blood-corpuscles become more and more filled with them. Simultaneously there make their appearance in the interior of the plasmodia pigment granules, which are derived from the coloring-matter of the blood. When the plasmodia attain a certain size the pigment granules collect in the centre, while at the same time a radiating cleavage sets in, so that daisy-like figures are produced (*f*, *g*). These consist of a pigmented centre and radiating petals devoid of pigment. Later on, the petals become detached from the central pigmented portion and assume a circular shape (*h*).

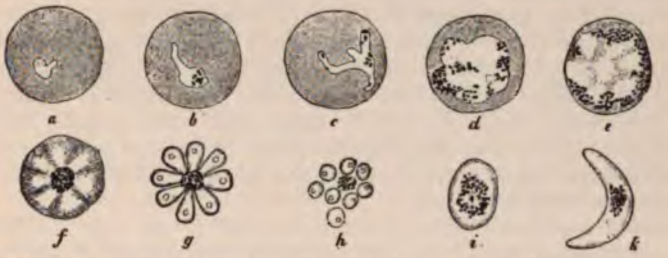


FIG. 456.—*Plasmodium malariæ* of a febris quartana in various stages of development. (After Golgi.) *a*, Red blood-corpuscle with a small, non-pigmented plasmodium; *b*, *c*, *d*, *e*, Pigmented, variously sized plasmodia inside of red blood-corpuscles; *f*, Plasmodium at the commencement of segmentation, with pigment collected in centre; *g*, Segmented plasmodium; *h*, Plasmodium divided into separate globules; *i*, *k*, Two differently shaped, free plasmodia.

According to Golgi, this development and segmentation of the plasmodia in febris quartana is complete in three days, and the attacks of fever set in at the time when the plasmodia are dividing. The red blood-corpuscles which are occupied by the plasmodia perish; the young plasmodia just formed by cleavage again penetrate the blood-corpuscles, whereupon their further development begins anew. The pigment granules formed by the plasmodia, some free, others inclosed in cells, are carried out of the circulating blood into various organs, especially the spleen, liver, and marrow of the bones.

In *febris tertiana* the cycle of development is complete in two days (Golgi). The plasmodia developing within the red blood-corpuscles (Fig. 457, *a*, *b*, *c*, *d*) show much livelier motion and at the same time lead very much more rapidly to a decoloration of the red blood-corpuscles than in the febris quartana, so that the latter are already decolorized on the first day of intermission of the fever, while the plasmodia are still small. The protoplasm of the plasmodia of the febris tertiana is, furthermore, more delicate and less sharply defined, and their pigment granules are also smaller. In its division each plasmodium splits up into from fifteen to twenty new cells (*e*), while in the quartan fever only from six to twelve develop. Finally, the red blood-corpuscles in the febris quartana are mostly crenated, while in the tertian form they retain their shape. According to Celli and Marchiafava, the formation of spores not infrequently occurs prematurely, from five to ten spores developing inside of a red blood-corpuscle.

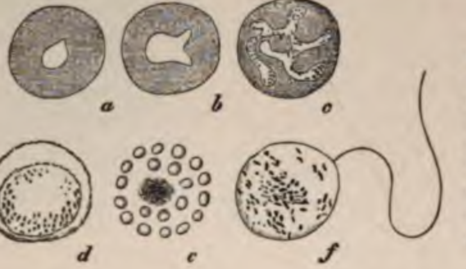


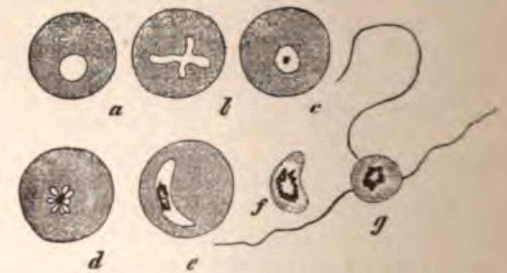
FIG. 457.—*Plasmodium malariæ* of a febris tertiana in various developmental stages. (After Golgi.) *a*, First step in development; *b*, *c*, Enlarged plasmodia with pseudopods; *d*, Plasmodia before the formation of spores—blood-corpuscle decolorized; *e*, Formation of spores; *f*, Free parasite with flagella.

In *febris quotidiana* (late-summer and fall fever, febris subcontinua, perniciosa) the parasite (Fig. 458) consists, according to Celli and Sanfelice, of small structures exhibiting lively amœboid movements inside the red blood-corpuscles (*a*, *b*); shortly before each new febrile attack they become pigmented and round (*c*), and then divide into spores (*d*).

According to Celli and Marchiafava, nuclear bodies may be demonstrated in the protoplasm in all endoglobular hæmatozoa of malaria, in certain stages of their development.

Besides the forms already described, which are considered by Italian authors as typical, there occur in the different malarial diseases in addition both endoglobular and free parasites, either oval or sickle-shaped (Fig. 456, *i*, *k*, and Fig. 458, *e*, *f*), sometimes provided with flagellæ (Fig. 457, *f*, and Fig. 458, *g*), at other times having cast these off; and all these forms, especially described by Laveran, have been since confirmed by the Italian authors.

FIG. 458.—*Plasmodium malariæ* of a febris quotidiana in various stages of development. (After Celli and Sanfelice.) *a*, First step in the development; *b*, Plasmodia with pseudopods; *c*, Plasmodium which has become round and provided with pigment before segmentation; *d*, Formation of spores; *e*, Intraglobular crescent form; *f*, *g*, Free plasmodia.



The significance of all the various forms of parasites which have been observed in malaria has not yet been fully solved; nevertheless, from the preceding statements it may be considered settled that the endoglobular hæmatozoa destroy the red blood-corpuscles and thus manufacture pigment out of the coloring-matter of the blood; and it may also be assumed that their presence gives rise to the morbid symptoms of malaria.

Laveran is of the opinion that all the forms described belong to one and the same diversely shaped sporozoön, while the Italian authors (Golgi, Canalis, Celli, Marchiafava) believe that there are various malaria parasites. They consider that the free crescent forms and the flagella plasmodia should be regarded as sterile forms of vegetation which are not able to reproduce themselves by spore-formation, but sooner or later perish.

The plasmodia may be taken up by leucocytes in the various stages of their development, and this occurs principally at the beginning of the febrile attack (Golgi), at which time the plasmodia undergo segmentation. The leucocytes may contain plasmodia, accordingly, either entire or segmented, or, indeed, only the pigment masses.

The particular varieties of plasmodia correspond, according to the reports, to particular forms of fever, but yet it must be noticed that the febrile forms designated as febris quotidiana, subcontinua, and comitata may also be caused by the existence in the blood of plasmodia of the tertian or quartan form in various generations, so that part of the parasites reach spore-formation each day. In this way arise quotidian forms of fever which are to be considered as double tertian (quotidiana triquartanaria).

According to Golgi, there is also a malarial fever (summer and fall fever) the parasites of which develop not in the blood, but in the internal organs, especially in the marrow of the bones.

Within the organs of patients who have died of malaria there are found, first of all, the malaria parasites containing pigment, and lying more or less intravascularly. If the blood has undergone great destruction there will also be found pathological deposits of iron in the spleen, liver, medulla of the bones, and the kidneys. In consequence of the deposition in the spleen of products of blood-degeneration, and also of malaria parasites containing pigment (part of which are inclosed in leucocytes), there occur in this organ considerable swellings, accompanied by hyperæmia, which lead in part to tissue-degeneration, in part to tissue-hypertrophy. After the process has continued some time the spleen may become greatly enlarged, pigmented, and much changed in structure. There may also ensue in the liver, on the one hand, degeneration and pigmentation of its parenchyma, and, on the other hand, new growths which lead to induration.

According to the investigations of Danilewsky, Celli, Marchiafava, Grassi, Feletti, Crookshank, Laveran, and others, there not infrequently occur protistæ in the blood of mammalians and birds, as well as in that of cold-blooded animals, and among them some which resemble the *Plasmodium malariæ* very closely and undergo a similar cycle of development inside the red blood-corpuscles. The closest resemblance of characteristics is seen in the hæmatozoa of birds (pigeons, owls, magpies, and larks); but even these show some variation, so that they are not the same form of parasite as is observed in man.

According to Celli, only the spores can live in the blood-plasma in man, while the other grades of development, in case they leave the blood-corpuscles for the plasma, are destroyed, forming flagellæ, swelling up, and becoming vacuolated. On the other hand, the hæmatozoa of birds can exist in the plasma for a certain length of time, and the hæmatozoa of the cold-blooded animals, whose development progresses very slowly, live a good while free in the blood; and these forms which exist free in the blood are the ones which have been described as special parasites (drepanidium).

The systematic classification of the plasmodia of malaria, and the protozoa which are nearly related to them, is not yet arranged. Most probably they are to be classified with the Sporozoa; and since the forms which occur in the muscles have received the name of sarcosporidia, the parasites of blood-corpuscles, belonging to the class last considered, might be called hæmosporidia (Danilewsky).

INDEX.

ABRACHIUS, 412.
Abrin, poisoning by, 24.
Abscess, burrowing, 300.
  chronic, 300.
  congestive, 300.
  formation of, 277.
  healing of, 293.
Acardiacus, 425.
Acarus folliculorum hominis, 536.
  scabiei, 535.
Acervuloma, 345.
Achirus, 412.
Achorion Schönleini, 529.
Acids, corrosive, action of, 19.
Aconitin, poisoning by, 26.
Acrania, 402.
Actinomycosis, 510.
Addison's disease, 60.
Adenia, simple and leucæmic, 335.
Adenocarcinoma, 357.
  medullary, 363.
Adenocystoma, 357, 376, 384.
Adenoma, 351, 352.
  alveolar, 352.
  malignum, destruens, or carcinomatosum, 357.
  papilliferum, 352.
  tubular, 352.
  umbilicale, 409.
Adhesions of serous membranes, formation of, 289.
Agenesia, 142, 159.
Agnathia, 406.
Air in the blood or tissues, effects of, 47.
Akromegaly, 218.
Albumin, products of the putrefaction of, 437.
Albuminoids, protective, 73.
Alcohol, poisoning by, 25.
Alexins, 73.
Algor mortis, 144.
Alkaloids, cadaveric, 33.
Allantoic cloaca, 412.
Amelus, 412.
Amnion, pathological conditions of, causing malformation of the embryo, 387.
Amœba coli mitis, 563.
    vulgaris, 563.
  dysenteriæ, 564.
Amputation neuromata, 255, 332.
Amyloid degeneration, 180.
Anæmia, acute, effect of, upon the circulation, 106.
  chronic, effect of, upon the circulation, 106.
  general, 143.
  local, 112.
Anasarca, 129.
Anchylostoma duodenale, 542.
Androgynes, 421.
Anencephalia, 403.
Aneurism, cirsoid, 324.
Angioma, 320.
  arterial, 324.
  cavernous, 322.
  hypertrophic, 321
  lymphatic, 324.
  varicose, 322.
Angiomyoma, 327.
Angiosarcoma, 342.
Anguillula intestinalis, 545.
  stercoralis, 544.
Anhydræmia, effect of, upon the circulation, 106.
Aniline, poisoning by, 24.
Animals, poisons derived from, 20.
Anthrax, bacillus of, 462.
  symptomatic, bacillus of, 506.
Antitoxins, 74, 76.
Anus, atresia of, 412.
Aphthæ, 525, 527.
Aplasia, 142.
Aprosopia, 405.
Apus, 412.
Arachnida, parasitic, 534.
Area medullo-vasculosa, 398.
Argyria, 213.
Arrhinencephalia, 404.
Arteries, chalky concretions in the, 124.
Arterioliths, 124.
Arthrospores, 433.
Ascaris lumbricoides, 540.
  mystax, 541.
Ascites, 130.
  chylous, 140.
Ascococci, 431, 447.
Aspergilli, 528.
Asphyxia, definition of, 9.
  local, 147.
Atavism, 96.
Atheromata of the skin, 407.
  development of cysts from, 375.

Atresia oris, 407.
Atrophy, 142, 159.
  active, 164.
  degenerative, 163.
  excentric, 160.
  fatty, 168.
  from disuse, 165.
  from impaired nutrition, 164.
  from pressure, 165.
  neuropathic, 165.
  pigment, 169.
  senile, 164.
  serous, of fat-tissue, 169.
  simple, 163.
Atropin, poisoning by, 26.
Attraction-spheres, 229.
Autoblasts, 163.
Auto-intoxications, 49.
Awlworm, 541.

BACILLI, 431, 459.
  pathogenic, 462.
Bacillus aceticus, 462.
  acidi lactici, 461.
  anthracis, 462.
  blackleg, 506.
  butyricus, 461.
  caucasicus, 461.
  chicken-cholera, 509.
  coli communis, 470.
  comma, 517.
  cyanogenes, 461.
  diphtheriæ, 472.
  diphtheriæ columbarum, 510.
  fluorescens liquefaciens, 461.
  influenza, 472.
  lepræ, 498.
  mallei, 503.
  murisepticus, 510.
  œdematis maligni, 475.
  pneumoniæ, 470.
  pneumonicus agilis, 472.
  prodigiosus, 461.
  pyocyaneus, 462.
  rhinoscleroma, 505.
  saprogenes, 462.
  subtilis, 460.
  swine-erysipelas, 508.
  symptomatic anthrax, 506.
  syphilis, 492.
  tetani, 474.
  tuberculosis, 476.
  typhi abdominalis, 467.
  ureæ, 462.
  xerosis, 506.
Bacteria, 431.
  actinomyces, 510.
  ascococci, 447.
  attenuation of pathogenic properties of, 442.
  bacilli, 459.
  bacillus aceticus, 462.
    acidi lactici, 461.
    anthracis, 462.
    blackleg, 506.
    butyricus, 461.
Bacteria, bacillus aceticus, caucasicus, 461.
    chicken-cholera, 509.
    coli communis, 470.
    comma, 517.
    cyanogenes, 461.
    diphtheriæ, 472.
    diphtheriæ columbarum, 510.
    fluorescens liquefaciens, 461.
    influenza, 472.
    lepræ, 498.
    mallei, 503.
    munisepticus, 510.
    œdematis maligni, 475.
    pneumoniæ, 470.
    pneumonicus agilis, 472.
    prodigiosus, 461.
    pyocyaneus, 462.
    rhinoscleroma, 505.
    saprogenes, 462.
    subtilis, 460.
    swine-erysipelas, 508.
    symptomatic anthrax, 506.
    syphilis, 492.
    tetani, 474.
    tuberculosis, 476.
    typhi abdominalis, 467.
    ureæ, 462.
    xerosis, 506.
  bacterium coli commune, 470.
    termo, 462.
  biology, 431.
  chemical changes caused by, 437.
  chemotactic properties of certain, 436.
  cladothrix asteroides, 515.
  cocci, 446.
  comma-bacillus, 517.
  crowding out of one variety by another, 436.
  cultivation of, 443.
  different forms of, 446.
  diplococci, 446.
  diplococcus pueumoniæ, 455.
  effect of antiseptic substances upon, 437.
    of cold upon, 434.
    of heat upon, 434.
    of light upon, 434.
  examination of, 443.
  gonococcus, 454.
  inconstant pathogenic properties of, 441.
  leptothrix buccalis, 462.
  merismopedia, 447.
  micrococci, 447.
  micrococcus gonorrhœæ, 454.
    pyogenes tenuis, 450.
    tetrogenus, 448.
  mode of entrance of, into the system, 33.
  monomorphic, 431.
  nitrifying, 438.
  nutrition of, 433.
  oligomorphic, 431.
  pathogenic, 31, 440.
    inoculation of attenuated, 83.
    natural protection of the organism against, 69.

Bacteria, pleomorphic, 432.
proteus vulgaris, 462.
ray-fungus, 510.
saprophytic cocci, 447.
sarcinæ, 447.
specific poison of, 37.
spirilla, 516.
spirillum choleræ Asiaticæ, 517.
Finkler-Prior, 521.
rubrum, 517.
rugula, 516.
sputigenum, 521.
tenue, 516.
tyrogenum, 521.
undula, 516.
volutans, 516.
spirochaete buccalis sive denticola, 516.
Obermeieri, 522.
plicatilis, 516.
staphylococci, 447.
staphylococcus pyogenes albus, 450.
pyogenus aureus, 448.
pyogenus citreus, 450.
steam more efficacious than dry heat in the destruction of, 434.
streptococci, 447.
streptoccus erysipelatis, 453.
pyogenes, 450.
streptothrix Maduræ, 515.
substances hindering the development of, 435.
suppuration, 278.
vibrio Metschnikovi, 522.
rugula, 516.
serpens, 516.
Bacterium coli commune, 470.
termo, 462.
Balantidium coli, 565.
Barrel-figure, 229.
Basement substance of the tissues, 248.
Bedbugs, 538.
Bed-sores, 148.
Bioblast, 163.
Biting-mite, 537.
Blackleg, bacillus of, 506.
Blennorrhœa, 276.
Blisters, formation of, 268, 270.
Blood, air in the, 47.
atrophic, condition of the, 143.
change in, producing fatty degeneration, 171.
coagulation of the, 115.
disturbances in the circulation of the, 103.
extravasation of, 134.
changes in color in, 200.
fluidity, no value in the diagnosis of the mode of death, 122.
protective albuminoids of the, 73.
stasis of, 128.
Blood-cells, life of the, 251.
red, new formation of, 249.
white, new formation of, 248.
Blood-plates, 251.
conglutination and viscous metamorphosis of, 119.
Blood-plates, the product of the red blood-corpuscles, 121.
Blood-poisons, 21.
Blood-serum of immunized animals, therapeutic use of, 84.
Blood-tumor, 134.
Blood-vessels, new formation of, 241.
of granulation tissue, 284.
Body-louse, 538.
Bone, formation of, 248.
regeneration of, 245.
Bothriocephalus cordatus, 563.
latus, 561.
Brachygnathia, 406.
Burns, 11.

CACHEXIA, definition of, 143.
of tumors, 311.
suprarenal, 60.
thyreopriva, 58.
Calcification, 188.
Calculi, tertiary, 193.
bronchial, formation of, 193.
formation of, 188.
organic nuclei of, 193.
urinary, 194.
Cancer, see *Carcinoma.*
Cancer-cells, 361.
Carbon disulphide, poisoning by, 24.
monoxide, poisoning by, 22.
Carcinoma, 351, 357.
adenomatosum, 357.
alveolar, 364.
colloid, 364.
cylindrical epithelial, 362.
cylindromatosum, 365.
degenerative processes in, 368.
etiology of, 369.
flat-celled epithelial, 362.
gelatinous, 364.
giant-celled, 366.
medullon, 362, 363.
metastases of, 367.
myxomatous, 365.
parasitic theory of, 370, 570.
retrograde changes in, 368.
scirrhosum, 362, 363.
simplex, 362, 363.
umbilication of, 369.
Caro luxurians, 301.
Cartilage, formation of, 248.
hyaline, regeneration of, 246.
Caseation, 281.
Castration, effects of, upon the organism, 61.
Catarrh, 268.
chronic, 299.
desquamative, 270.
mucous, 270.
purulent, 276.
serous, 270.
Caterpillars, fungi producing disease in, 533.
Caustics, 19.
Cebocephalia, 404.
Cell-body, two elements of, 235.

Cell-growth, influences affecting, 238.
Cells, cancer, 361.
  cloudy swelling of, 166.
  division of, budding, 235.
  division of, changes preparatory to, 227.
    protoplasmic constriction in, 229.
  giant, 234.
    in tuberculosis, 478.
  hydropic degeneration of, 167.
  irritability of the, 238.
  mast, 163.
  nucleus the centre of power for the, 234.
  phagocytosis of, 68, 71.
  proliferating power of the, 236.
  resting, 236.
  tactile irritability of, 71.
Centrosomes, 229.
Cephalocele, 404.
Cercomonas intestinalis, 565.
Cerebrospinal canal, deficient closure of, 396.
Cestodes, 552.
Chancre, 493.
Charcot's crystals, 178.
Cheilo-gnatho-palatoschisis, 405.
Chemotaxis, 71, 296.
  affecting emigration of leucocytes in inflammation, 263.
  in relation to bacteria, 436.
Chemotropismus, see *Chemotaxis*.
Chicken-cholera, bacillus of, 509.
Chloral hydrate, poisoning by, 25.
Chloroform, poisoning by, 24.
Chloroma, 345.
Cholera, Asiatic, spirillum of, 517.
  nostras, spirillum of, 521.
Cholera-red, 518.
Cholesterin, 173.
Chondroblasts, 245.
Chondroma, 316.
Chondromyxoma, 314, 348.
Chondromyxosarcoma, 348.
Chondrosarcoma, 317, 348.
Chromatin, 227.
Chromosomes, 228.
Chylangioma, 325.
Chyluria, 140.
Cicatrization, 226.
Cicutoxin, poisoning by, 26.
Cimex lectuarius, 538.
Circulation, corporal, changes of vascular resistance in, 107.
  general disturbances of the, 103.
  inflammatory disturbances of the, 261.
  pulmonary, changes of vascular resistance in, 108.
Cirrhosis of the liver, 302.
Cladothrix asteroides, 515.
Cleft palate, 405.
Climate, influence of, upon man, 30.
Clostridium, 431, 460.
Clothing-louse, 538.
Clots, lardaceous, 115.
  post-mortem, 114.
Cloudy swelling, 166.
Clubbed hand, 416.
Club-foot, 415.
Coagulation of the blood, 115.
Coagulation-necrosis, 149, 151.
Cocci, 431, 446.
  pathogenic, 448.
  saprophytic, 447.
Coccidia, 566.
Colchicine, poisoning by, 26.
Cold, disease caused by, 12.
"Colds," 13.
Colloid cancer, 364.
  degeneration, 178.
Concretions, amyloid, 185.
  formation of, 188.
  urinary, 194.
Condyloma, acuminate, 299.
Congestion, 109.
Conglutination of blood-plates, 119.
Conidia spores, 524.
Coniine, poisoning by, 26.
Connective tissue, hyperplasia of, 244.
  regeneration of, 244.
Contagium, definition of, 29.
Corpora amylacea, 185.
Corpulence, 169.
  inherited predisposition to, 90.
Crab-louse, 538.
Crab-pest, cause of, 533.
Cranial vault, deficiency in the, 402.
Craniopagi, 424.
Craniorachischisis, 397, 402.
Cranioschisis, 402.
Cretinism, 59.
Criminal, the congenital, 91, 96.
Crisis, definition of, 64.
Cruor, definition of, 114.
Cryptomerorachischisis, 401.
Culture methods of examining for bacteria, 443.
Curarine, poisoning by, 26.
Cyanosis, 105.
Cyclencephalia, 404.
Cyclocephalia, 404.
Cyclopia, 404.
Cylindroma, 346.
Cystadenoma, malignant papillary, 378, 380.
Cysticercus cellulosæ, 555.
  racemosus, 556.
Cystocarcinoma, papillary, 378, 380.
Cystofibroma, papillary, 380.
Cystoma, development of, 376.
  epithelial, 351, 371.
  multilocular, of the ovary, 371.
  of the breast, 375.
  of the kidney, 374.
  of the liver, 373.
  of the ovary, 371.
  of the skin, 375.
  of the testicle, 373.
  papillary, of the breast, 375.
    of the ovary, 373.
  simple, 373.
  unilocular, 371.

Cystomyxoma, papillary, 381.
Cystosarcoma, 375.
  papillary, 381.
Cysts, bronchial, 407.
  due to capsule-formation around foreign body, 216.
    liquefaction of a portion of tissue, 216.
  echinococcus, 558.
  formation of, 213.
  formed by parasites, 216.
  hydatid, 559.
  retention, 213.
Cytoblasts, 163.

DAUGHTER-STARS, 229.
Death, 143.
  apparent, 145.
  local, 145.
  signs of, 144.
Death-spots, 112.
Decubitus, 148.
Deformities, 386.
Degenerate, the, 91, 96.
Degeneration, amyloid, 180.
  cheesy, 150.
  colloid, 178.
  fatty, 170.
  granular, 166.
    of cells, 163.
  hyaline, 186.
  hydropic, 167.
  lardaceous, 180.
  mucous, 176.
  of tissue, causes of, 142.
  parenchymatous, 166.
  waxy, 150, 180.
Demodex folliculorum hominis, 536.
  in dogs and swine, 537.
Derencephalia, 403.
Dermatocoptes, 537.
Dermatocysts, 383, 384.
Dermatomycosis diffusa flexorum, 533.
  furfuracea, fungus of, 531.
Dermatophagus, 537.
Dermoid cysts, 383, 407.
Desmobacteria, 431.
Desmoid tumor, 312.
Development, disturbances of, 386.
Diabetes mellitus, production of, 56.
Diapedesis, cause of, 135.
Diastematomyelia, 401.
Diathesis, hæmorrhagic, 136.
Digitalin and digitalein, poisoning by, 27.
Diphtheria, bacillus of, 472.
Diphtheritic inflammation, 279.
Diplococci, 431, 446.
Diplococcus pneumoniæ, 455.
Dipygus, 429.
Disease, acquired, transmission of, to descendants, 96.
  anatomical conception of, 3.
  causes of, 4.
    altered gland function, 55.
    animal parasites, 39.
    aspergilli, 528.
Disease, causes of, bacilli, 459.
    bacteria, 31, 446.
    cocci, 446.
    coccidia, 566.
    cold, 12.
    conceptional infection, 102.
    disturbances of circulation, 103.
    dust, 15, 43.
    electric discharges, 14.
    fatigue, 10.
    fission-fungi, 31, 446.
    heat, 11.
    increased atmospheric pressure, 14.
    insufficiency of oxygen, 8.
    intra-uterine placental, 102.
    lack of food and water, 9.
    mechanical influences, 15.
    mould-fungi, 523.
    poisoning, 17.
    protozoa, 563.
    reduced atmospheric pressure, 13.
    retrograde disturbances of nutrition and infiltration of the tissues, 142.
    spirilla, 516.
    thread-fungi, 529.
    yeast-fungi, 523.
  constitutional, 4.
    arising from internal causes, 89.
  definition of, 2.
  duration of, 5.
  general, 4.
  hæmatogenous, caused by metastasis, 41.
  immunity from, 79.
  infectious, 28.
    hereditary transmission of, 101.
  inheritable, 95.
  intrinsic causation of, 88.
  local, 4, 48.
    arising from internal causes, 90.
    effect of, upon the organism, 49.
    infectious, 38.
  lymphogenous, caused by metastasis, 41.
  metastatic, 41.
  miasmatic-contagious, 29.
  natural cure of, 95.
    protection against, 68, 79.
  nervous, of accidental origin, 16.
  objective symptoms of, 2.
  parasitic, 29.
  predisposition to, 77.
    inherited, 93.
  symptoms of, 2.
    subjective, 2.
  termination of, 5.
  transmission of, by inheritance, 95.
Distoma felineum, 551.
  hæmatobium, 551.
  hepaticum, 550.
  lanceolatum, 551.
  pulmonale, 550.
  sibiricum, 551.
Distomia, 407.

Dochmius duodenalis, 542.
Dracunculus medinensis, 548.
Dropsy, 129.
Duplicitas anterior, 427.
  posterior, 428.
Dust, diseases caused by, 15, 43.
Dwarf-growth, 395.
Dwarfs, 156.
  development of, 89.
Dyscrasia, bacterial, 37.
  definition of, 143.
Dysentery, amœba of, 564.

ECCHONDROSIS, 317.
Ecchymoses, 134.
Echinococcus, 557.
  granulosus, 559.
  hydatidosus, 559.
  multilocularis, 559.
  veterinorum, 559.
Ectopia cordis, 409.
  intestini, 409.
  vesicæ urinariæ, 409.
Eczema marginatum, fungus of, 530.
Effusions, inflammatory, 268.
Egyptian chlorosis, 542.
Electric stroke, disease caused by, 14.
Elephantiasis, 218.
  simulated by cirsoid neuromata, 334.
Embolism, 127.
  crossed or paradoxical, 42.
  formation of, 127.
  in the causation of disease, 40.
Embolus, a straddling, 45.
Embryo, malformation of the, 386.
  normal or pathological qualities present in the, are transmissible, 98.
  variations in the, 98.
Emphysema, gangrenous, 154.
  of the skin, 47.
Empyema, 276.
Encephalomeningocele, 403, 404.
Enchondroma, 316.
Endothelioma, 341.
Enostosis, 317.
Enterocysts, 384.
Enteroliths, 193.
Ephelides, 325.
Epidemic, definition of, 28.
Epigastrius, 426.
Epignathus, 426.
Epispadias, 411.
Epistaxis, definition of, 134.
Epithelial tumors, 303, 351.
Epithelioma, 362.
  contagiosum, 567.
Epithelium, horny degeneration of, 259.
  regeneration of, 239.
Ergotism, 21.
Erysipelas, streptococcus of, 453.
Erythrasma, 533.
Erythroblasts, 251.
Ether, poisoning by, 25.
Ethmocephalia, 404.
Eustrongylus gigas, 542.
Exostosis, 317.
Exostosis, cartilaginous, 319.
  connective-tissue, 320.
Exstrophy of the bladder, 409.
Extravasations of blood, 134.
  changes in color in, 200.

FARCY, bacillus of, 503.
Fastigium of fever, 64.
Fatigue, disease resulting from, 10.
Fats in the human body, 173.
Fat-tissue, serous atrophy of, 169.
Fatty atrophy, 168.
  degeneration, 170.
  granule-spheres, 295.
  neck, 316.
  tissue, formation of, 248.
Favus, fungus of, 529.
Felt-louse, 538.
Fermentation processes caused by bacteria, 437.
Fever, 62.
  stages of, 63.
  varieties of, 64.
Fibrin-ferment, derivation of, 121.
Fibroblasts, 245, 284.
Fibrolipoma, 315.
Fibroma, 312.
  œdematous, 314.
Fibromyoma, 328.
Fibromyxoma, 314.
Fibrosarcoma, 336, 340.
Filaria hæmatica, 549.
Filaria, medinensis, 548.
  papillosa, 549.
  sanguinis, 141, 548.
Fish, poisonous, 18.
Fission-fungi, 431. See *Bacteria*.
Fistula colli congenita, 407.
  lymph, 140.
Fistulous tracts, 277.
Fissura abdominalis, 409.
  sterni, 409.
Flea, 538.
Flies, 538.
  fungus producing disease in, 533.
Fœtus, bacterial invasion of, from the mother, 441.
  frog, 402.
  papyraceus, 425.
  syphilis of the, 498.
  tubercular infection of, from the mother, 490.
Foot-and-mouth disease, streptococcus of, 459.
Foreign bodies, formation of giant-cells around, 296.
Fragmentation, direct and indirect, in nuclear division, 233.
Freckles, 325.
Frog fœtus, 402.
Fungi, budding, 523.
  fission, 431.
  mould, 523.
  yeast, 523.

GALL-STONES, composition of, 193.

Gangrene, black, 153.
    chemical end-products of, 156.
    cold, 154.
    dry, 153.
    hot, 154.
    marasmic, 148.
    moist, 154.
    white, 154.
Gas-phlegmon, 278.
Gastrophilus, 539.
Gastroschisis, 409.
Genitalia, development of the, 418.
    external, malformations of the, 410.
Germ, variations in the, 98.
Germ-centres, 248.
Giant-cells, 234.
    surrounding foreign bodies, 296.
Giant-growth, 218, 416.
Giants, development of, 89.
Glanders, bacillus of, 503.
Glioma, 330.
Glycogen, deposit of, in the tissues, 174.
Gnats, 538.
Gonococcus, 454.
Gonorrhœa, micrococcus of, 454.
Gout, inherited predisposition to, 90.
    uric-acid deposits in, 190.
Granulation growths, chronic, 300.
    tissue, 282.
        cells of, 284.
Granulations, fungous, 300.
Granulomata, 301.
Gregarinæ, parasitic, 566.
Growth, abnormal, of the body, 89.
    dwarf, 395.
    giant, 218, 416.
    Guinea-worm, 548.
Gumma, 494.
Gynæcomastia, 418.

HÆMANGIOMA, 320.
Hæmangiosarcoma, 342.
Hæmatemesis, definition of, 134.
Hæmatoblasts, 251.
Hæmatocele, definition of, 134.
Hæmatocysts, 385.
Hæmatoidin, 202.
Hæmatoma, 134.
Hæmatometra, definition of, 134.
Hæmatopericardium, 134.
Hæmaturia, definition of, 134.
Hæmochromatosis, 200, 204.
Hæmofuscin, 206.
Hæmoglobin, derivatives of, 201.
Hæmoglobinæmia, 204.
Hæmoglobinuria, 204.
    of cattle, coccus of, 458.
Hæmophilia, 136.
Hæmoptysis, definition of, 134.
Hæmorrhage, 134.
    per diabrosin, 134.
    per diapedesin, 134.
    per rhexim, 134.
Hæmorrhagic diathesis, 136.
    exudate in inflammation, 274.
Hæmosiderin, 202.
Hæmosporidia, 574.
Hæmothorax, definition of, 134.
Harelip, 406.
Harvest-mite, 535.
Head-louse, 538.
Healing powers of the human body, 75.
Health, definition of, 1.
Heart, results of inefficient action of the, 104.
    thrombosis of the, 122.
Heart-poisons, 24.
Heart-polypi, 123.
Heat, disease caused by, 11.
Heat-stroke, 11.
Height of individuals, average, 221.
Helleborin, poisoning by, 27.
Heredity, atavistic, 96.
    collateral, 95.
    degenerative, 94.
    direct, 95.
    identical, 94.
    in the causation of disease, 93.
    transformational, 94.
Hermaphrodism, 392, 418.
    varieties of, 421.
Hernia cerebri, 404.
    umbilical, 409.
Herpes tonsurans, fungus of, 530.
Heteroplasia, 226.
Hippomelanin, 199.
Hodgkin's disease, 335.
Hog-cholera, bacillus of, 509.
Holorachischisis, 396.
Holoschisis, 233.
Homo delinquens, 91, 96.
Horns, epidermal, 222.
Horse-flies, 538.
Hyaline degeneration, 186.
Hydatids, 559.
Hydrazine, poisoning by, 23.
Hydrencephalocele, 404.
Hydrocele colli congenita, 407.
Hydrocyanic acid, poisoning by, 22.
Hydrogen sulphide, poisoning by, 22.
Hydromeningocele, 400.
Hydrorachis externa circumscripta, 400.
Hydrothorax, chylous, 140.
Hygroma colli congenitum, 325.
Hyoscyamine, poisoning by, 26.
Hyperæmia, active, 110.
    local, 109.
    passive, 110.
    venous, 105.
Hypermastia, 418.
Hyperonychia, 223.
Hyperostosis, 317.
Hyperplasia, localized, 225.
    of connective tissue, 244.
    of epithelium, 239.
Hyperthelia, 418.
Hypertrichosis, 222.
Hypertrophy, compensatory, 224, 241.
    definition of, 217.
    from failure of a variable organ to diminish in size, 225.
    from lessened wear, 224.

- Hypertrophy, from overwork, 223.
  - from repeated irritation, 225.
  - glandular, 355.
  - of congenital origin, 217.
  - of muscle, 253.
  - numerical, 226.
  - simple, 226.
- Hyphæ, 524.
- Hypoplasia, 142, 156.
- Hyposarca, 129.
- Hypospadias, 411.
- Hypostasis, post-mortem, 112.

- ICHTHYOSIS, 221.
  - congenita, 222.
  - hystrix, 222.
- Icterus, 208.
  - neonatorum, 212.
  - purely hæmatogenous, does not exist, 211.
- Idiosyncrasy, congenital and acquired, 78.
- Immunity, 79.
  - acquired, 82.
    - duration of period of, 88.
    - transmission of, from mother to child, 102.
  - natural, not transmissible by inoculation, 88.
  - through an attack of a specific disease, 82.
  - through injection of protective serum, 84.
  - through inoculation of attenuated bacteria, 83.
- Impetigo contagiosa, fungus of, 531.
- Inclusio fœtalis, 427.
- Infarcts, anæmic, 137, 139.
  - hæmorrhagic, 134, 138.
- Infection, bacterial, 440.
  - conceptional, 102.
  - cryptogenic, 36.
  - disease arising from, 28.
  - double, 441.
  - intra-uterine placental, 102.
  - mixed, 36.
  - natural protection against, 69.
  - parasitic, 30.
  - secondary, 36, 441.
- Infiltrations, amyloid, 185.
- Inflammation, 260.
  - acute, 260.
  - adhesive, 289.
  - atrophy of specific and hypertrophy of connective tissue in, 302.
  - by continuity, 261.
  - catarrhal, 268.
  - causes of, 260.
  - chemotaxis in, 296.
  - chronic, 297.
  - circulatory disturbances in, 261.
  - croupous, 270.
  - diphtheritic, 279.
  - ectogenous, 261.
  - effusions in, 268.
  - excretory, 261.
  - exudation in, 263.
- Inflammation, fibrinous, 270.
  - forms of, 260.
  - hæmatogenous, 261.
  - hæmorrhagic exudate in, 274.
  - infiltration of the tissues in, 266.
  - interstitial, 267.
  - lymphogenous, 261.
  - metastatic, 261.
  - necrotic, 278.
  - nomenclature of, 268.
  - parenchymatous, 267.
  - phagocytosis in, 294, 297.
  - process of repair associated with, 281.
  - proliferating, 282.
  - purulent, 275.
  - removal of the excitant of, 282.
  - superficial, 267.
  - suppurative, 275.
  - vascular changes in, 261.
- Influenza, bacillus of, 472.
- Infusoria, parasitic, 563.
- Inoculation, protective, 83.
- Insects, parasitic, 537.
- Insolation, 11.
- Intoxication, 17.
  - auto-, 49.
  - in infectious diseases, 33, 49.
- Invasion-disease, definition of, 39.
- Ischæmia, 112.
- Ischiopagi, 424.
- Itch-mite, 535.
- Ixodes ricinus, 536.

- JANICEPS, 428.
- Jaundice, 208.

- KARYOBLASTS, 163.
- Karyokinesis, 227.
- Karyomitosis, 227.
  - atypical, 232.
- Keratosis follicularis, 570.
- Kidney, contracted, 302.

- LARDACEOUS degeneration, 180.
- Leiomyoma, 327.
- Lentigines, 325.
- Leontiasis leprosa, 500.
- Leprosy, bacillus of, 498.
- Leptothrix, 431, 432.
  - buccalis, 462.
- Leptus autumnalis, 535.
- Leucæmia, 249.
- Leucoblasts, 251.
- Leucocytes, new formation of, 248.
  - of granulation tissue, 284.
- Leucocytosis, 249.
- Leyden's crystals, 178.
- Lice, 538.
- Lightning-stroke, effects of, 14.
- Lipochrom, 199.
- Lipofibroma, 315.
- Lipoma, 315.
- Lipomatosis, 168.
- Lipomyxoma, 314.
- Liquefaction necrosis, 151.
- Lithocelyphopædion, 395.
- Lithocelyphos, 395.

Lithopædion, 395.
Liver, cirrhosis of the, 302.
Liver-leach, 550.
Lungs, pigmentation of, by inhalation of dust, 212.
Lupus, 484.
Luxations, congenital, 415.
Lymph, obstruction to flow of, not succeeded by œdema, 131.
Lymphadenoid tissue, formation of, 247.
Lymphadenoma, 334.
Lymphangioma, 320, 324.
Lymphangitis, miliary tubercular, 487.
Lymph-fistula, 140.
Lymph-glands as barriers against infection, 72.
Lymphoma, 336.
Lymphorrhagia, 140.
Lymphosarcoma, 335, 338.
Lysins, 74.
Lysis, definition of, 64.

MACROCHEILIA, 325.
Macroglossia, 325.
Macrostomia, 407.
Madura foot, fission-fungus of, 515.
Maggotworm, 541.
Malanders, 537.
Malaria, parasite of, 570.
Malformations, 386.
  atavistic, 387.
  atypical, 388.
  causes, 387.
  congenital, 386.
  double, 387, 392, 423.
  due to abnormal disposition of parts, 392.
    abnormal positions of internal organs and extremities, 415.
    defective development, 391.
    deficient closure of cerebrospinal canal, 396.
    excessive growth, 391, 416.
    faulty closure of abdominal and thoracic cavities, 408.
    multiplication of parts, 416.
    partial duplication of axial structures, 427.
    pathological conditions of the amnion, 387.
    persistence of fœtal structures, 384, 392.
    presence of tissues in unusual situations, 381, 392.
  exhibiting mixture of sexual characteristics, 392.
  hermaphrodism, 418.
  inherited, 387.
  of external genitalia, 410.
  of extremities due to arrest of development, 412.
  of face and neck, 405.
  of mouth, 407.
  of nervous system, 396.
  single, 386, 391.
  typical, 388.
Marasmus, definition of, 143.
Margarin crystals, 173.
Marrow, bone-formation of, 247.
Mast-cells, 163.
Measle of bothriocephalus latus, 562.
  of tænia solium, 555.
Meckel's diverticulum, persistence of, 409.
Megastoma entericum, 565.
Melanin, 197.
Melanocarcinoma, 366.
Melanosarcoma, 344.
Membrane, croupous formation of, 271.
Meningocele, 400, 403, 404.
Meningococcus, 457.
Meningo-encephalocele, 404.
Menorrhagia, definition of, 134.
Merismopedia, 431, 432, 447.
Merorachischisis, 397.
Metaglobulin, derivation of, 121.
Metakinesis, 229.
Mataplasia, epithelial, 259.
  tissue, 257.
Metastasis, bodies producing, 42.
  carcinoma, 367.
  in the causation of disease, 40.
  of neoplasms through the blood-vessels, 309.
    through the lymph-channels, 308.
  retrograde, 42.
Methæmoglobin, 23.
Methæmoglobinuria, 204.
Metrorrhagia, definition of, 134.
Miasm, definition of, 29.
Micofibroma of horses, ascococcus of, 459.
Micrencephalus, 156.
Microbacteria, 431.
Microbrachius, 412.
Microcephalus, 156, 403.
Micrococci, 431, 447.
Micrococcus fœtidus, 448.
  gonorrhœæ, 454.
  pyogenes tenuis, 450.
  tetragenus, 448.
Micromelus, 412.
Micro-organisms, 31, 431, 563.
Microprotein, 432.
Micropus, 412.
Microsomia, 395.
Microsporon furfur, 531.
  minutissimum, 531.
Microstomia, 407.
Miescher, sacs of, 569.
Milk-patch, 289.
Mites, parasitic, 534.
Mitom, 235.
Mitosis, 227.
  asymmetrical, 232.
  bipolar and multipolar, 231.
Moles, 394.
Monas lens, 565.
Monilia candida, 528.
Monobrachius, 412.
Monopus, 412.
Monsters, 386.
  autosite, 425.

Monsters, double, 387, 392, 423.
    origin of, from a single egg, 392.
  parasitic, 425.
  single, 391.
  triple-headed, 430.
Morphine, poisoning by, 26.
Mother-star, 228.
Mould-fungi, 523.
  saprophytic, 525.
Mouse-septicæmia, bacillus of, 510.
Mucins, 177.
Mucor corymbifer, 527.
Mucorineæ, disease-producing, 37.
Mucous degeneration, 176.
Mucous-tissue, formation of, 247.
Mummification necrosis, 153.
Musca anthropophaga, 539.
Muscardine in silkworms, fungus of, 533.
Muscarine, poisoning by, 27.
Muscle, hypertrophy of, 253.
  regeneration of, 251.
Mushrooms, poisoning by, 23, 27.
Mussels, poisonous, 18.
Mycelium, 524.
Mycetoma, fission-fungus of, 515.
Mycoderma albicans, 528.
Myelocystomeningocele, 400.
Myelocysts, 384.
Myelomeningocele, 399.
Myiasis, 538.
Myofibroma, 328.
Myoma, 327.
  striocellulare, 329.
Myosarcoma, 330.
Myxochondroma, 314.
Myxœdema, resemblance of, to thyreoprival cachexia, 58.
Myxofibroma, 314.
Myxolipoma, 314.
Myxoma, 314.
Myxosarcoma, 314, 347.

NÆVUS, lymphatic, 325.
  pigmentosus, 325.
  pilosus, 325.
  prominens, 325.
  spilus, 325.
  vascular, 320.
  verrucosus, 325.
Nanosomia, 395.
Necrobiosis, 147, 151.
Necrosis, 145.
  anæmic, 147.
  causes of, 146.
    bacterial, 279.
    chemical, 278.
  chemical end-products of, 156.
  coagulation, 149, 151.
  diphtheritic, 279.
  direct, 147.
  indirect, 147.
  inflammatory, 278.
  liquefaction, 151.
  marasmic, 148.
  mummification, 153.
  repair after, 290.
Necrosis, results of, 148.
  senile, 148.
  sequelæ of, 148.
Nematodes, 539.
Neoplasm, see *Tumor*.
Nerve-poisons, 24.
Nerve-tissue, regeneration of, 254.
Neuroglia, regeneration and hypertrophy of, 254.
Neuroglioma ganglionare, 331.
Neuroma, 332.
  amputation, 255, 332.
  cirsoid, 334.
  plexiform, 334.
Neuroses, traumatic, 16.
Neurotization, 257.
New-born, causation of disease in the, 81.
  uric-acid infarction of the, 195.
New-growth, see *Tumor*.
Nicotine, poisoning by, 26.
Nitro-bacteria, 438.
Nitrous oxide, poisoning by, 25.
Nuclear framework, 227.
  segments, 228.
Nuclein, 227.
Nucleus, division of, 227.
    amitotic, 233.
  structure of a completely developed, 227.
  the centre of power for the cell, 234.
Nutrition, retrograde disturbances of, 142.

OBESITY, 169.
  inherited predisposition to, 90.
Ochronosis of cartilage, 200.
Odontoma, 317.
Œdema, 129.
  cachectic, 132.
  ex vacuo, 133.
  hydræmic, 132.
  inflammatory, 132, 269.
  malignant, bacillus of, 475.
  of stagnation, 131.
  purulent, 278.
  varieties of, 131.
Œstrus ovis and bovis, 539.
Oïdium albicans, 527.
Old age, predisposition of, to disease, 81.
Omphalocele, 409.
Omphalopagi, 423.
Onychogryphosis, 223.
Onychomycosis favosa, 530.
  tonsurans, 530.
Opium, poisoning by, 25.
Organs, average weight of, 221.
  supernumerary, 416.
Ostéoarthropathie hypertrophiante, 219.
Osteoblasts, 245.
Osteochondroma, 317, 350.
Osteofibroma, 349.
Osteoma, 317.
Osteophyte, 317.
Osteoporosis, 160.
Osteosarcoma, 349.
Oxyuris vermicularis, 541.

PACHYAKRIA, 218.
Paget's disease, parasite of, 570.
Papillary excrescences in cysts, development of, 377.
Papilloma, 312.
Paramæcium coli, 565.
Paramitom, 235.
Paraplasm, 235.
Parasites, animal, 39, 534.
  micro-, 30, 431, 563.
  pathogenic, 29, 446.
Parrots, death of, from infection with streptococcus mycosis, 459.
Pathology, general, definition of, 6.
Pearl-disease in cattle, 491.
Pediculi, 538.
Penis, duplication of the, 411.
Pentastoma, 536.
  in cattle, 537.
Perobrachius, 412.
Perochirus, 412.
Peromelus, 412.
Peropus, 412.
Pes calcaneus, 415.
  equinovarus, 415.
  valgus, 415.
Pestilence, definition of, 28.
Petechiæ, 134.
Petrifaction, 188.
Phagocytosis, 68, 71, 294, 297.
Phallin, poisoning by, 23.
Phenyl hydrazine, poisoning by, 23.
Phimosis, hypertrophic, 411.
Phleboliths, 124.
Phlegmon, formation of, 278.
Phlogosis, see *Inflammation.*
Phocomelus, 412.
Phymatorhusin, 199.
Picric acid, poisoning by, 24.
Pigment, autochthonous, 197.
  formation of, in the tissues, 197.
  hæmatogenous, 200.
  introduction of, from without, 212.
  origin of, 197.
Pigmentation, 197.
Pigmented-granule spheres, 295.
Pithead, 561.
Pityriasis rosea, 533.
  versicolor, fungus of, 531.
Plasmodium malariæ, 570.
Plethora, effect of, upon the circulation, 107.
Pleuropneumonia of cattle, bacteria of, 458.
Pneumococcus, 457.
Pneumonia, bacillus of, 470.
  diplococcus of, 455.
Poisons, blood, 21.
  classification of, 19, 27.
  disease caused by, 17.
  insusceptibility to, 79.
  list of the most common, 17.
Polar furrow, 398.
Polydactylism, 417.
Polymelia, 429.
Polypi, hairy, 383.
Polypi, heart, 123.
Potassium chlorate, poisoning by, 23.
  cyanide, poisoning by, 22.
Predisposition to disease, 77.
    at different ages, 81.
    racial, 82.
    sexual, 82.
Prepuce, abnormalities of, 411.
Proliferation in inflamed tissue, 282.
Prosoposchisis, 406.
Protein, immunity-, 76.
Proteus vulgaris, 462.
Prothrombin. 121.
Protophytes, 431.
Protoplasm, division of, 234.
  structure of, 234.
Protozoa, pathogenic, 39, 563.
Pseudomelanosis, 203.
Pseudomucin, 177.
Pseudorhabditis stercoralis, 544.
Pseudotuberculosis cladothrichica, 515.
  guinea-pigs, caused by cocci, 459.
Psorospermose folliculaire végétante, 570.
Ptomaïnes, 33, 437.
Pulex irritans and penetrans, 538.
Pulsation, venous, cause of, 105.
Pulse, accelerated, in fevers, 66.
Pus, calcification of inspissated, 293.
  formation of, 275.
Pus-cocci, 448.
Pustule, formation of, 277.
Putrefaction, caused by bacteria, 437.
  post-mortem, 145.
Pyæmia, 451.
  cryptogenetic, 452.
Pyelonephritis of cattle, bacillus of, 509.
Pygopagus, 428.
Pyosepthæmia, 451.
Pyrexia, see *Fever.*
Pyrogallol, poisoning by, 23.

QUININE, poisoning by, 26.

RACHIPAGUS, 428.
Rachischisis, 396.
Rainey's bodies, 569.
Ray-fungus, 510.
Refrigeration, disease resulting from, 11.
Regeneration, 217.
  following inflammation, 281.
  incomplete, 226.
  of blood-cells, 248.
  of connective tissue, 244.
  of epithelium, 239.
  of muscular tissue, 251.
  of nerve-tissue, 254.
  of neuroglia, 254.
Relapsing fever, spirochaete of, 522.
Retention-disease, 50.
Rhabdomyoma, 329.
Rhinoscleroma, bacilli of, 505.
Ricine, poisoning by, 24.
Rigor mortis, 144.
Rigors, 65.
Rouget du porc, bacillus of, 508.
Roundworms, 539.

SACCHAROMYCES, ellipsoideus, 525.
Saccharomycetes, disease-producing, 37.
Sago-spleen, 180.
Sand-flea, 538.
Santonin, poisoning by, 26.
Saprophytes, 433, 523.
Sarcinæ, 431, 432, 447.
Sarcoma, 336.
  alveolar, 340, 352.
  giant-celled, 340.
  mucoid or hyaline degeneration in a, 346.
  osteoid, 349.
  phyllodes, 381.
  polymorphous-celled, 340.
  round-celled, 337.
  spindle-celled, 339.
  tubular, 340.
Sarcoptes hominis, 535.
    in horses and sheep, 537.
  minor, 537.
  squamiferus, 537.
Sarcospores, 569.
Scabies, parasite of, 535.
Schistoprosopia, 405.
Schizomycetes, 30, 431. See *Bacteria.*
Scirrhus, 363.
Scleroma respiratorium, bacilli of, 505.
Sclerosis of connective tissue, 187.
Segmentation, direct and indirect, in mitosis, 233.
Septhæmia, 457.
Septicæmia, 450.
Septicopyæmia, 451.
Sequestration of necrosed tissue, 282.
Serum, immunizing, 84.
Shock, 15.
  erethistic, 16.
  torpid, 16.
Silkworms, fungus producing disease in, 533.
Skin, multiple fibromata of the, 333.
  transplantation of, 236.
  tumors of the, belonging to the lymphangiomata, 325.
Somatoblasts, 163.
Sphacelus, 154.
Sphærobacteria, 431.
Spina bifida, 399.
  occulta, 400, 401.
Spinal column, deficient closure of, 396.
Spinal cord, division of, in rachischisis, 401.
Spirilla, 431, 516.
  choleræ Asiaticæ, 517.
  Finkler-Prior, 521.
  pathogenic, 517.
Spirillum sputigenum, 521.
  tyrogenum, 521.
Spirobacteria, 516.
Spirochaete, 431, 516.
  buccalis sive denticola, 516.
  Obermeieri, 522.
  plicatilis, 516.
Spoolworm, 540.
Spore-formation of fission-fungi, 432.
Spores, conidia, 524.
Sporozoa, parasitic, 566.
Staphylococci, 431, 447.
Staphylococcus pyogenes albus, 450.
    aureus, 448.
    citreus, 450.
Starvation, disease resulting from, 9.
Sternopagi, 424.
Strangles in horses, coccus of, 458.
Streptococci, 431, 432.
Streptococcus erysipelatis, 453.
  pyogenes, 450.
Strongylus duodenalis, 542.
  longevaginatus, 544.
  varieties infesting animals, 544.
Strychnine, poisoning by, 26.
Sucking-mite, 537.
Sucking-worms, 549.
Suffocation, death from, 9.
Suffusions, bloody, 134.
Suggillations, 134.
Sun-stroke, 11.
Supernumerary organs or parts of the body, 416.
Suppuration, 275.
  bacteria causing, 278, 448.
Suprarenal capsules, disease of the, 60.
Swelling, cloudy, 166.
Swine-erysipelas, bacillus of, 508.
Swine-pest, bacillus of, 509.
Swine-plague, bacillus of, 509.
Sycosis parasitaria, 530.
Symbiotes equi, 537.
Symmelia, 412.
Sympus, 412.
Syncephalus, 424, 428.
Syncope, 16.
Synophthalmia, 404.
Synotia, 406.
Syphilis, bacillus of, 492.
  congenital, communicated by either parent, 101.
  hereditary, 496.

TÆNIA cœnuris, 561.
  cucumerina, 557.
  echinococcus, 557.
  mediocanellata, 557.
  nana, 557.
  saginata, 557.
  solium, 553.
Tail, formation of a, 418.
Talipes, 415.
Talipomanus, 416.
Tapeworms, 552.
Tartar of the teeth, 193.
Tattooing, 212.
Temperature, increased body-. See *Fever.*
Teratomata, 304, 381, 426, 428, 429.
  autochthonous, 384.
  explanation of, 384.
  heterochthonous, 384.
Tetanus, bacillus of, 474.
Tetany, thyreoprival, 58.
Thallophytes, classification of the, 523.
Thoracogastroschisis, 409.

Thoracopagi, 423.
Thoracopagus parasiticus, 426.
Thoracoschisis, 409.
Threadworm, 541.
Thrombin, derivation of, 121.
Thrombo-arteritis purulenta, 125.
  phlebitis purulenta, 125.
Thrombosis, 115.
  of small vessels, origin of, 124.
Thrombus, autochthonous, 123.
  blood-plate, 118.
  calcification of a, 124.
  dark-red, 116.
  formation of a, 117.
  free globular, in the heart, 123.
  induced, 123.
  laminated, 117.
  marasmic, 122.
  obturating, 123.
  organization of a, 125.
  parietal, 123.
  primary, 123.
  replacement of, by connective tissue, 290.
  septic softening of a, 125.
  softening of a, 124.
  valvular, 123.
  white, 117.
Thyroid gland, disease resulting from decreased or suspended function of the, 58.
Tinea favosa, fungus of, 529.
Tissue, connective, hyperplasia and regeneration of, 244.
  embryonic, formation of, 245.
  fatty, formation of, 248.
  formative, 235.
  granulation, 284.
  infiltrations of, 142.
  influences restricting growth of, 238.
  law of specific character of the, 235.
  lymphadenoid, formation of, 247.
  metaplasia of, 257.
  mucous, formation of, 247.
  transposition of germs of, 385.
Tissue-growth, inflammatory, 283.
Tissue-transplantation, 236.
Toluylendiamine, poisoning by, 23.
Tongue, black hairy, 222.
Tophi, gouty, 192.
Torula-chains, 447.
Toxalbumins, 33, 37, 437.
Toxinprotein, immunity-, 76.
Toxins, 33.
Toxopeptone, cholera, 520.
Transplantation, skin-, 236.
  tissue, 236.
Trematodes, 549.
Tricephalus, 430.
Trichina spiralis, 545.
Trichocephalus dispar, 545.
Trichomonas intestinalis and vaginalis, 565.
Trichophyton tonsurans, 530.
Triplets, homologous, 430.
Trophoneuroses, 54.
Tubercle, caseation of, 480.
Tubercle, lymphoid, 479.
  metastatic, 489.
  miliary, 482.
  retrograde changes in, 479.
Tuberculin, 481.
Tuberculosis, bacillus of, 476.
  cure of, 487.
  formation of caverns in, 484.
  miliary, 489.
  of birds, 492.
  of cattle, 491.
  primarily a local disease, 481.
  pseudo-cladothrichica, 515.
    in guinea-pigs, caused by cocci, 459.
Tumors, 303.
  adenocarcinoma, 357.
  adenocystoma, 357.
  adenoma, 351, 352.
  angioma, 320.
  angiomyoma, 327.
  angiosarcoma, 342.
  appositional growth, 306.
  benignant, 311.
  blood-, 134.
  cachexia of, 311.
  carcinoma, 351, 357.
  cartilaginous, 316.
  cavernous, 322.
  chloroma, 345.
  chondroma, 316.
  chondromyxoma, 314.
  chondrosarcoma, 317.
  chylangioma, 325.
  cirsoid aneurism, 324.
  connective-tissue, 303, 336.
  cylindroma, 346.
  cystoma, 351, 371.
  definition of, 303.
  dermoid, 383.
  desmoid, 312.
  development through proliferation of tissue-cells, 305.
  enchondroma, 316.
  endothelioma, 341.
  epithelial, 303, 351.
  epithelial cystoma, 351, 371.
  epithelioma, 362.
  etiology of, 306.
  fatty, 315.
  fatty neck, 316.
  fibrolipoma, 315.
  fibroma, 312.
  fibromyoma, 328.
  fibromyxoma, 314.
  fibrosarcoma, 336, 340.
  glioma, 330.
  growth of, by infiltration, 308.
  hæmangioma, 320.
  hæmangiosarcoma, 342.
  heteroplastic, 305.
  histoid, 303.
  homœoplastic, 305.
  interstitial expansive growth of, 306.
  leiomyoma, 327.
  lipofibroma, 315.

Tumors, lipoma, 315.
  lipomyxoma, 314.
  lymphadenoma, 334.
  lymphangioma, 320, 324.
  lymphatic, 324.
  lymphosarcoma, 335, 338.
  malignant, 311.
  medullary, 303.
  melanocarcinoma, 366.
  melanosarcoma, 344.
  metastases of, 306.
  mixed forms, 348.
  mucous, 314.
  muscular, 327.
  myofibroma, 328.
  myoma, 327.
  myosarcoma, 330.
  myxochondroma, 314.
  myxofibroma, 314.
  myxolipoma, 314.
  myxoma, 314.
  myxosarcoma, 314, 347.
  nævus, 320.
  necrosis of, 310.
  nervous, 330.
  neuroglioma ganglionare, 331.
  neuroma, 332.
  number, 304.
  organoid, 304.
  osteochondroma, 317.
  osteoma, 317.
  papilloma, 312.
  psammoma, 345.
  recurrence of, 311.
  retrogressive changes in, 310.
  rhabdomyoma, 329.
  sand, 345.
  sarcoma, 336.
  scirrhus, 363.
  secondary, 306.
  structure of, 303.
  telangiectasia, 320.
  teratoid, 381.
  teratomata, 381, 426, 428, 429.
  the type of heteroplastic growth, 226.
  transplantation of, 310.
  varieties of, 312.
  vascular, 320.
Twins, homologous, 423.
Typhoid fever, bacillus of, 467.

Udder, inflammation of, caused by streptococcus, 458.

Ulcer, atonic, 300.
  callous, 300.
  cancerous, 369.
  chronic, 300.
  formation of, 277.
  indolent, 300.
  serpiginous, 300.
  syphilitic, 495.
  tuberculous, 488.
Umbilication of cancer, 369.
Ureteritis cystica, probable parasitic origin of, 570.
Urethra, atresia of, 411.
Uric-acid deposits, 190.
  infarction of the new-born, 195.

Vaccination, an example of acquired immunity, 82.
Vacuoles in tissue-elements in inflammation, 267.
Variations, hereditary, Weismann's theory of, 100.
  in the germ or embryo, 98.
Vascular resistance, increased, 107.
Veins, chalky concretions in the, 124.
  pulsation in the, cause of, 105.
Veratrine, poisoning by, 26.
Verruca carneæ, 326.
Vesicles, formation of, 268, 270.
Vibrio Metschnikovi, 522.
Vibrios, 431, 516.
Viscera, lateral transposition of, 415.

Warts, fleshy, 326.
  ichthyotic, 222.
Waxy degeneration, 180.
Weight of individuals, average, 221.
  of organs, average, 221.
Whipworm, 545.
Wood-tick, 536.
Worms, parasitic, 539.
Wound-diphtheria, 280.
Wounds, healing of, 285.

Xerosis conjunctivæ, bacillus of, 506.
Xiphopagi, 423.

Yeast-fungi, 37, 523.

Zona dermatica, 398.
  epithelo-serosa, 398.
Zoöglœa, 432, 447.

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